CHAPTER XVI

DISEASES OF THE BONES

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Part I

OSTEITIS DEFORMANS (PAGET'S DISEASE)

Introduction

Historical.—The first description of osteitis deformans was given by Sir James Paget[50], who in 1876 presented to the Medico-Chirurgical Society of London a paper entitled "On a Form of Chronic Inflammation of Bones (Osteitis Deformans)." He reported five cases and gave a masterly description of the clinical picture, symptoms and signs, as well as of the pathology of the disease. So complete and accurate is Paget's account of the disease that comparatively little has since been added to our knowledge of the malady. In a second paper published in 1882 Paget[51] recorded further observations on these cases and reported seven additional ones. Thirteen years after his first communication he stated in a short report that he had observed a total of twenty-three cases.

In his original paper Paget describes the disease as follows: "It begins in middle age or later, is very slow in progress, may continue for many years without influence on the general health, and may give no other trouble than those which are due to the changes of shape, size, and direction of the diseased bones. Even when the skull is hugely thickened, and all its bones exceedingly altered in structure, the mind remains unaffected.

"The disease affects most frequently the long bones of the lower extremities and the skull, and is usually symmetrical. The bones enlarge and soften, and those bearing weight yield and become unnaturally curved and misshapen. The spine, whether by yielding to the weight of the overgrown skull, or by change in its own structures, may sink and seem to shorten with greatly increased dorsal and lumbar curves; the pelvis may become wide; the necks of the femora may become nearly horizontal, but the limbs, however misshapen, remain strong and fit to support the trunk.

"In its earlier periods, and sometimes through all its course, the disease is attended with pains in the affected bones, pains widely various in severity and variously described as rheumatic, gouty, or neuralgic, not especially nocturnal or periodical. It is not attended with fever. No characteristic conditions of urine or faeces have been found in it. It is not associated with syphilis or any other known constitutional disease, unless it be cancer.

"The bones examined after death show the consequences of an inflammation affecting, in the skull the whole thickness, in the long bones chiefly the compact structure of their walls, and not only the walls of their shafts but, in a very characteristic manner, those of their articular surfaces."

Medical literature previous to 1876 contains reports of cases which may be examples of osteitis deformans but the description of the condition is so meager as to make the diagnosis very doubtful. As early as 1801 Saucerotte[64] described the case of a man who died at forty and whose bones generally were enlarged. A similar instance of hypertrophy of nearly the whole skeleton in a man who died at seventy was published by Rullier[63] in 1809. From the meager description given, Paget considers these cases as doubtful. Wrany[76], in 1867, recorded a case of a woman of fifty with "spongy hypertrophy of the cranium, atrophy of the face, spongy hypertrophy of the spine, pelvis and left lower leg with elongation." He summarizes the process as a "rarefying osteitis with softening." Paget regarded this case as probably a true example of osteitis deformans.

The only undoubted example of the disease described prior to Paget was published by Wilks[75] in the Transactions of the Pathological Society of London in 1869. It is the same as case 4 of Paget's series. Czerny[8], in 1873, under the title "Eine lokale Malacie des Unterschenkels" records a case of a man of twenty-two years who showed local softening and deformity in the lower tibia and fibula, and reviewed six other similar cases collected from the literature. The disease is evidently not one of Paget's type but the report is of interest as Czerny first used the term "osteitis deformans" to describe the condition.

Synonyms.—A considerable array of formidable names, for the most part in accordance with the author's conception of the pathology of the disease, have been applied to this condition. A list of the most common of these terms is as follows: osteitis deformans (Paget); Paget's disease; osteomyelitis fibrosa (v. Recklinghausen); ostéomalacie locale (D'Ollier); sclerose osseuse hypertrophique (Menetrier and Gauckler); osteomalacia chronica deformans hypertrophica (Schmieden); osteitis ossifiante diffuse (Lancereaux); megalo-osteomyelitis fibrosa (Ganiciero); ostéolyose (Lobstein); spongiöse knockenhypertrophie craniosclerosis (Huschke); ostéomalacie hypertrophique bénigne (Vincent); hyperostose generalisee, osteite condensante (Volkmann); pseudo-rachitisme sénile (Pozzi); rhumatisme ostéo-hypertrophique des diaphyses et des os plats (Féreol); diffuse hyperostosis. The disease is usually and most appropriately designated as osteitis deformans or Paget's disease.

Definition.—A chronic progressive disease of the skeleton usually beginning in middle life which leads to a symmetrical and usually painful thickening and bowing of the long bones as well as hypertrophy and deformity of the skull and other units of the skeleton.

Incidence.—Osteitis deformans is usually classified among the rare diseases and the small number of cases reported since Paget's first publication seems to bear out this opinion. Hurwitz[23] found only three cases

among over 30,000 medical admissions to the Johns Hopkins Hospital, and DaCosta the same number in 38,000 admissions to the Jefferson Hospital, Philadelphia. Higbee and Ellis[20] found 158 cases in the literature to 1910. In 1914 DaCosta, Funk, Bergeim and Hawk[9] collected fifty more which had been subsequently published and added five personal observations making in all 213 cases to 1914. The disease is, however, by no means so rare as these facts would indicate. The subjective symptoms are very seldom prominent or severe and in consequence the patient very seldom enters a hospital and in my experience is almost invariably found in the clinic suffering from some other malady. Furthermore, in a majority of cases the typical changes in the bones are revealed by X-ray examination of the skeleton when not otherwise suspected. During the past twenty years I have personally studied forty-eight cases and have probably seen as many more. With the exception of syphilis, osteitis deformans is the most common of the chronic bone diseases.

Etiology

The cause of the disease is unknown. Numerous theories variously based on clinical, histological, chemical and bacteriological characteristics of the disease have from time to time been advanced to explain the osseous changes. The most important of these possible etiologic factors may be grouped as follows: (1) gout, (2) rheumatism, (3) bacterial infection and trauma, (4) malignant disease, (5) disorders of the endocrine glands, (6) syphilis, (7) trophic nerves, (8) heredity, (9) arteriosclerosis.

1. Among the cases in England the presence of gout has been so common as to suggest some significant connection with osteitis deformans as an etiologic factor. Paget and Hutchinson[25] especially call attention to the frequent association of the two. The fact that gout is so prevalent in England and that the disease is exceedingly rare in association with osteitis as observed in other countries would seem definitely to disprove that the disease is the result of gout. A history of gout was obtained but once in my personal series.

2. The hypothesis that osteitis deformans is to be regarded as due to or a form of rheumatism has many advocates especially among the French writers. Huchard and Binet[21] were the first to suggest that the disease is of rheumatic origin. Lancereaux[32] and Richard[61] attempted to prove that osteitis deformans and arthritis deformans are very closely related if not identical. A close study of the published cases as well as my own gives no evidence of any such relationship either in the character of the symptoms recorded or the association of the two conditions.

3. Paget in his original article concludes that the disease is to be regarded as an inflammation of the bones. Hutchinson[26] is of the opinion that the disease "begins in consequence of contusion of one bone which spreads by infection to others." A few cases, but too few to carry weight, have been reported where a relationship of the disease to an antecedent injury to the bone is suggested. Chastel[7] collected fifty cases and in only twelve was there any history of trauma however remote. He admits that trauma may localize the disease as in tuberculosis but contends that it is never the actual but only a possible auxillary cause. Previous injury was never mentioned in any of my cases. Arcangeli[1] claims to have isolated an organism from the tibia of a woman with osteitis deformans but Ellis obtained negative results in two cases (quoted by DaCosta, Funk, Bergeim and Hawk). Critical study of the records of all reported cases by several authors has failed to furnish any justification for accepting either bacterial infection or trauma as causal factors.

4. The frequent association of osteitis deformans and malignant tumors is unquestioned. In 1889 Paget[52] states that of eight cases who were traced to the end of life five developed either cancer or sarcoma and on the basis of this experience takes the stand that the "intimate relation between osteitis deformans and malignant tumors is decisive." Fourteen of my series have died while under observation and three have shown this complication. Packard, Steele and Kirkbride[49] found cancer in four and one-half per cent. and sarcoma in seven and one-half per cent. of all cases to 1901. In all probability, as suggested by Negellen[48], the irritation resulting from the bony lesions in osteitis may favor the development of a neoplasm. He regards cancer as a contemporary disease of osteitis in the aged rather than the cause of it. In every instance it has occurred late in the course of the disease of the bones.

It is important to remember that osteitis deformans is almost invariably seen at the time of life when the incidence of malignant disease is the greatest. The duration of malignant disease is at most a few years while in the case of osteitis deformans life is often prolonged twenty or even thirty years after the development of bone deformity. That the coexistence of the two diseases is common must be admitted but so far as any definite etiologic relationship between the processes in the two diseases is concerned we have no evidence.

5. One of the most recent and plausible theories regarding the cause of osteitis deformans is that the bone changes result from some disturbance in the function of certain of the endocrine glands. That perverted function of the ductless glands may lead to definite and marked disorders of bone metabolism has been repeatedly proved. Several diseases showing characteristic bone changes are known to be due to such causes (acromegaly,

gigantism, cretinism). MacCallum and Voegtlin[42] have shown experimentally the influence of the parathyroids on the calcium metabolism. DaCosta, Funk, Bergeim and Hawk[9] found marked variations from the normal in the calcium, magnesium, phosphorus and sulphur metabolism in two cases of Paget's disease. The very nature of the process in the bones in osteitis as well as the general course of the disease strongly suggests that it may result from such perversion of glandular function.

On the other hand, pathological studies offer but little support for such an hypothesis. Abnormalities in the thyroid are recorded in but seven cases and these do not appear suggestive; sclerosis (Lévi[36, 37], Hudelo and Heitz[22], Higbee and Ellis[20]), atrophy (Pescarolo and Bertolotti[55], Lyons[41], Gruner, Scrimger and Foster[19]) and tumor (Askanazy[2]). The thyroids in a considerably greater number of cases were found normal. The adrenals were reported sclerotic in a single case (Hudelo and Heitz[22]). In the case reported by Bartlett[4] the hypophysis "showed a very striking preponderance of large polygonal (chromophile) cells over the small cuboidal cells." DaCosta, Funk, Bergeim and Hawk[9] noted in the X-rays a "calcareous deposit in the region of the pineal gland." After a very careful discussion of the subject Higbee and Ellis[20] conclude that "to suggest a disturbance in the internal secretions as a possible etiological factor, is to risk the accusation of adding without sufficient cause to an already overburdened theory of the disease."

6. One of the earlier views is that osteitis deformans is a late manifestation of hereditary syphilis (Lannelongue[33]). This theory has called forth wide discussion and has found many advocates especially among the French writers. Lannelongue based his theory on the close resemblance of the bone changes in cases of Paget's disease and those occurring in late syphilis as well as certain clinical resemblances in the symptoms and deformity of the legs. Fournier[12] strongly supports this theory. On the basis of an alleged identity of clinical characteristics in the osteopathies of infancy and childhood resulting from hereditary syphilis and osteitis deformans, he concludes that there is an identity of origin. Subsequent studies, however, by a large number of authors have differentiated the two conditions both clinically and by means of the X-rays. The majority of cases reported have shown no evidence whatsoever of the presence of syphilis nor in later years has the Wassermann test given positive results. Souques and Vallery-Radot[70] in 1913 published the results of a careful study of the Wassermann reaction in osteitis deformans. They were able to collect further cases in which the tests had been made and five were found positive. Weber[74] in 1908 showed conclusively that congenital syphilis affecting the bones could be sharply differentiated from osteitis deformans and nearly all writers of the past ten years hold the same view. None of my series of forty-eight cases gave any history or evidence of syphilis. A general review

of all reported cases also shows the presence of antecedent syphilis to be unusual. Furthermore, with very few exceptions many observers have used mercury and iodides in osteitis deformans with entirely negative results. Paget himself in his original publication mentions that he found no evidence that the disease was related to syphilis. Chastel[7] in 1910 reviewed the entire question of etiology and discussed exhaustively the evidence for and against hereditosyphilitic hypothesis. He concludes that the syphilitic theory is "alluring but not solid."

7. Several authors have sought to show that osteitis deformans is a distrophy of nervous origin. The frequent and characteristic changes in the bones occurring in such diseases of the central nervous system as syringomyelia and tabes have suggested by analogy that the bone changes in this disease may also be of a trophic nature due to some sort of nervous lesion. Lancereaux[32] first suggested that the nervous system may play a part in causing osteitis deformans. Three reported cases have shown sclerosis of the posterior columns of the cord (Gilles de la Tourette and Marinesco[15, 16, 17] two; Lévi[38], one). Slight macroscopical changes in the posterior columns were observed in Pic's[56] case. Stilling[71] and Lunn[40] report minor abnormalities in the spinal cord which do not seem significant. Further evidence in favor of this view is believed by some to be found in the work of Schiff[65] who produced trophic changes in the tibiae, fibulae and bones of the feet of dogs by section of the sciatic and crural nerves. From the reported results, however, the process induced seems to have been one of simple atrophy (Schirmer). A chronic myelitis was found in von Recklinghausen's[58] case. Hudelo and Heitz[22] described changes in the spinal cord and medulla but which they did not regard as significant. Prince[57] in 1902 reviewed the evidence exhaustively and concludes that the "lesions found in the spinal cord and peripheral nerves and analogy with other known lesions like those of tabes and syringomyelia suggest a neuropathic origin similar to that of the myopathies."

With the few exceptions cited above the central nervous system has always been found normal in cases of osteitis deformans. The lesions described have not been of any definite type and in several instances at least it seems reasonable to attribute them to arteriosclerosis. Evidence based on such irregular and unusual findings and the mere analogy to certain diseases of the central nervous system with bone lesions cannot be accepted as of much weight. Furthermore, if the disease were of neuropathic origin it would appear reasonable to expect some clinical evidence but this is entirely wanting. There is, therefore, little if any actual support for this hypothesis.

8. The part which heredity plays in this disease is somewhat difficult to determine. Paget[52] in 1889 states that he has "tried vainly to trace any

hereditary tendency" in his twenty-three cases. Most authors are inclined to this view. Smith[68], however, believes that the disease belongs to the family or inherited diseases. DaCosta, Funk, Bergeim and Hawk[9] collected 213 typical cases of osteitis deformans and among them found fifteen instances with positive family history, or seven per cent. In seven there were two cases in the same generation, and in seven two or more cases in two generations. In many of the published cases, however, no mention is made of family history and in all probability this point was not investigated in a majority.

Evidence of the existence of the disease in the same or previous generations was carefully sought for in all my cases with the result that in ten of a total forty-eight (twenty and eight-tenths per cent.) a definite positive history was obtained. Five cases were in two members of the same generation and five in parent and child. One of the latter group gave a typical history of the disease in both his father and paternal grandfather. Such figures cannot fail of significance though in how far heredity is a determining factor in causing the disease cannot be stated. Certain it seems that a family tendency in osteitis deformans is far more common than has generally been recognized and probably lies much nearer twenty than seven per cent.

9. The atheromatous theory of osteitis deformans has received much attention throughout the literature of the subject. More or less generalized arteriosclerosis, usually of a striking type, has been so commonly observed in these cases that it may almost be regarded as a universal manifestation of the disease. The interpretation to be placed on this association is difficult to determine. That atheromatous alterations in the arteries may lead to nutritive changes in osseous tissues is well recognized and has naturally led to the supposition that the association of arteriosclerosis with osteitis deformans is to be interpreted as the cause of the bone changes which characterize the disease. Béclère[5] suggests that the bone changes are due to extreme sclerosis of the nutrient arteries of the affected bones. The process in the bones associated with such vascular changes in a main trunk artery or the nutrient vessel are as a rule essentially those of atrophy. In my cases the intensely sclerosed arteries shown in the X-rays have not been confined to those of advanced years but are also to be seen in many of those observed in early middle life.

It is difficult to explain why if osteitis is due to arteriosclerosis the disease does not occur much more commonly considering the great frequency of the former condition at the period of life when osteitis most commonly develops. Lévi[38] raises the question if both the sclerosis and the process in the bones may not be due to some dystrophy of unknown cause.

It can hardly be doubted that the extreme degree of atheroma of the vessels so constantly met with must play some role etiologically and yet, as

Higbee and Ellis[20] say, "the possibility of vascular lesions possessing any specific influence in producing the disease appears very remote."

Age

Osteitis deformans is spoken of as a disease of advanced life but the figures given below indicate that in a majority of cases the disease begins before the fiftieth and rarely as early as the thirtieth year. As a rule, on the other hand, the patient does not consult a physician until many years later. Packard, Steele and Kirkbride[49], from a study of sixty-seven cases collected from the literature, give the average age at onset as forty-nine and a half years and the average age when first coming under observation as sixty-one. The forty-eight cases personally observed by me averaged forty-five and a half years at time of onset and fifty-seven at time of coming under observation. In only eleven instances did the first symptoms appear after fifty. The youngest case in my series was twenty-eight and the oldest sixty-seven. Several instances of the disease at ages varying from twelve to seventeen years are often quoted but a careful reading of the original reports has convinced me that none are genuine cases of Paget's disease. Moizard and Bourges[46] report one instance with symptoms first noted at twenty-one which seems to be a true example of osteitis deformans. Stilling[71] records a case which was first seen at age ninety-two.

Sex

Males are probably a trifle more commonly afflicted. Packard, Steele and Kirkbride[49] show sixty-five per cent., my series fifty-eight per cent. males.

Occupation and race appear to play no part.

Pathology

The pathology of this disease is primarily concerned with the osseous system. A wide variation in the character and degree of the bone changes is observed depending on the duration and extent of development of the process. Of whatever stage, however, the fundamental changes are unusually definite and constant.

The bones most commonly affected are those which give to the disease its peculiar deformity, namely, the skull and long bones of the legs and arms (Fig. 1). The great majority of cases show the first changes in the skull and tibia, which seem to be the starting point of general skeletal alterations.

Although much more common in the axial bones the process may affect any or all parts of the skeleton. A few examples are recorded where a systematic X-ray examination of the entire skeleton has shown a surprising number of bones with some degree of alteration.

The disease almost invariably shows a bilateral but very asymmetrical and irregular involvement. Klippel and Weil[29, 30] report a unique exception. The patient, a woman of fifty-six years, who had had symptoms for eleven years presented typical deformities of Paget's disease strictly confined to the right side of the skeleton.

The gross changes (Fig. 1) consist primarily in a general thickening and in the case of the long bones of a conspicuous bowing, both characteristics being in evidence throughout the shaft and in advanced stages involving the epiphysis as well. Not infrequently the bone is increased to twice its normal size. In all cases the bowing is in the nature of an accentuation of the normal curve together with a moderate degree of torsion. Actual lengthening also takes place. The normal ridges and prominences may be the first to show the hypertrophy. As the disease progresses the normal markings of the bone are gradually lost. The diseased bone appears plump and misshapen and has been likened in outer appearance to roughly hewn stone. The general outline is fairly regular but the surface is extremely uneven. Occasionally the even outline is broken by rather large osteophytic outgrowths. Such proliferation in a few instances may take the form of typical Heberden's nodes. These outer modifications are particularly common to the tibia, femur, fibula, humerus, radius and ulna. Paget[50] describes the general appearances of the long bones as follows:

"The outer surface of the walls of the bones was irregularly and finely nodular, as with external deposits or outgrowths of bone, deeply grooved with channels for the larger periosteal blood-vessels, finely but visibly perforated in every part for transmission of the enlarged small vessels. Everything seemed to indicate a greatly increased quantity of blood in the vessels of the bone."

The periosteum is deeply injected in many places and moderately adherent. On section the diseased bone presents a picture even more varied than in its outer aspects. The normal appearance is completely altered and in its place one finds an irregular, spongy, coral-like structure. In places the hypertrophied bony tissue is soft, very rich in blood and appears as very coarsely reticular tissue. Here and there particularly near the outer surface of the shaft are areas of the appearance and hardness of ivory. There is gross evidence of increase in the fat. When the process is advanced the medullary cavity is entirely obliterated by the coarse, irregular, newly formed osteoid tissue. The marrow where present is fibrous or fatty in type.

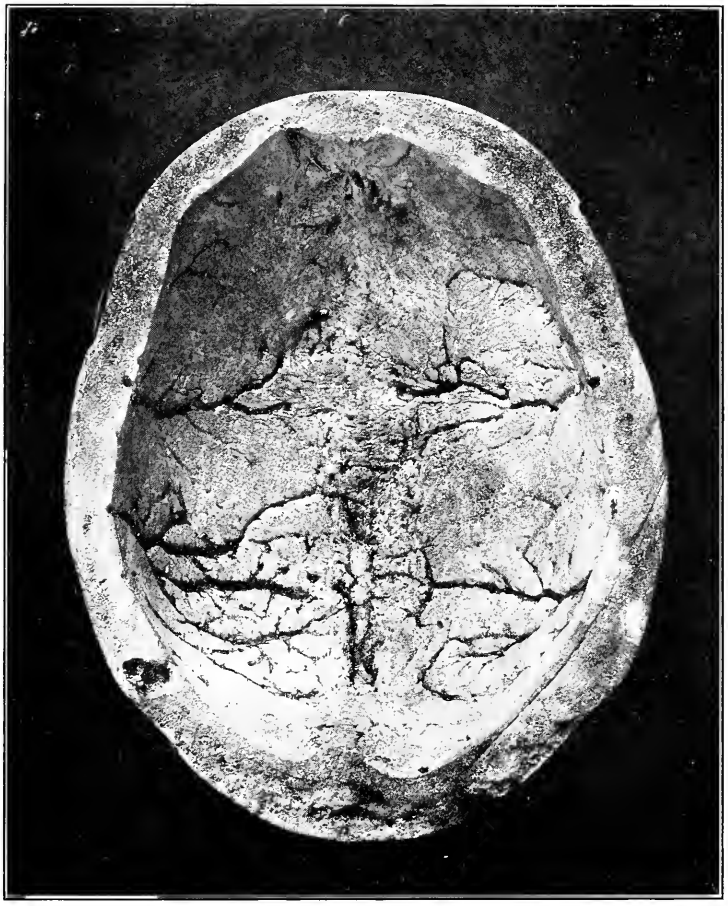

FIG. 1.—Osteitis deformans; calvarium from male, age 63. Note the great thickening, porous texture, roughened surface and deepening of the grooves for vessels.

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Rarely small spaces are seen in the shaft, seldom more than 1 or 2 cm. in diameter, filled with reddish gelatinous material. These are the bone cysts which occur with such a variety of bone diseases. These are always small in size, and may be single or multiple.

Butlin (see Paget[50]), who made the pathological studies on Paget's first cases, describes minutely the microscopical appearances. The Haversian systems and canals were much diminished in number but enormously widened and many were confluent, the communicating spaces being filled with blood vessels and ill developed tissue. The sides of these canals were not smooth but eaten out to form the so-called Howship's lacunae so characteristic of inflammation. New and incompletely developed bone was very evident beneath the periosteum. Fibrous tissue and fibrocells were abundant. The evident absorption of the original bone as well as its manner of absorption lead Butlin to consider the process as a true chronic inflammation.

Stilling[71] interprets the process in the bones as a rarefying osteitis beginning beneath the periosteum and gradually involving more central portions with its usual accompaniment of new bone formation which remains uncalcified. He agrees with Butlin in his interpretation of the process as essentially an inflammatory one.

Von Recklinghausen's[59] conception is that the first changes are in the nature of a simple osteomalacia with resulting destruction of cortical substance of the bone in consequence of which the bone bends. Following this there is an inflammatory process in the malactic areas which is characterized by a transformation of the fatty and lymph marrow into fibrous tissue from which a network of compact bone develops but which remains uncalcified for a long time.

Since these early papers many authors have discussed the changes in the bones and their nature. Very little, however, has been added to these original descriptions. The nature of the process is now accepted as a double one, namely, first, a lacunar absorption of bone by the osteoclasts (Askanazy[2]), and second, the formation of new "fibroosteoid" tissue which may at first be poor in lime salts and late in the disease become sclerotic. In other words, there is a double process of rarefaction (malacia) and new bone formation essentially of connective tissue origin. There seems good reason to doubt the explanation of the osseous changes as a true inflammation.

The widespread halisteresis in the bones possibly explains the bowing as well as the tendency to spontaneous fracture. The interpretation of the new bone formation as a reparative process or compensatory effort to strengthen the bone which has yielded to the strain of weight bearing or tension from muscle action seems incorrect. As von Recklinghausen and others have said the parts where the most marked proliferation occurs is not

at the point of the greatest value mechanically and is out of all proportion to the compensation needed. Furthermore, the same alterations take place in the skull and other bones as of the arms where the above named mechanical factors are not present. While it is impossible to deny that weight bearing may be one factor in causing the bowing in the bones of the legs it cannot be the chief one for the reasons just stated. In the case of every affected bone in osteitis deformans the bowing is strictly in the nature of an accentuation of the normal curve. The most natural explanation of the characteristic deformity is to be found in the extreme degree of general hypertrophy present in the bones which, because of the tendency to actual increase in length, induces the curve since the more or less fixed ends prevent any considerable longitudinal growth.

The changes in the skull (Fig. 2) are among the earliest and most striking observed in the skeleton. The whole calvarium is uniformly enlarged often to an extraordinary degree. In several cases under my observation the skull increased from 60 to 66 cm. in circumference as compared with a normal of 54 to 58 cm. One of Paget's cases measured 71 cm. The outer surface is fairly regular and symmetrical but with special prominence in the occipital, parietal and frontal regions. The sutures are often obscured. Frequently the mastoid processes of the temporal bones and the malar bones are prominent. In a few cases the bones of the face and especially the lower jaw show considerable hypertrophy although as a rule these bones remain unchanged. The skull cap cuts easily due to its soft and friable nature. All normal structural markings may be absent. As in the case of the long bones the tissue is rich in blood, soft and augmented in thickness. Islands of varying size of dense homogeneous bone are occasionally present. The frontal sinuses may be obstructed or entirely obliterated by new bone. The calvarium in a case reported by Pearce[53] measured one and one-half inches in thickness in the occipital region. The inner surface is more irregular and dense than the outer and is often closely adherent to the dura. The grooves for vessels are deep and the orifices voluminous.

Marie, Léri and Chatelin[44], Léri and Chatelin[35], and Regnault[60] have studied the base of the skull in Paget's disease and find very constant and striking alterations. They observed the same type of hypertrophy and deformity as seen in other parts of the skeleton and affecting all structures. As a result of the osseous hypertrophy there is a varying degree of narrowing of all foramina which give passage to vessels and nerves including the foramen ovale. Léri and Chatelin describe a "total depression of the skull under the weight of the brain" and an increase in the transverse and anteroposterior diameter of the cavity.

The spine in advanced cases is markedly changed. It is rigid throughout due to extensive ankylosis with a very pronounced kyphosis involving

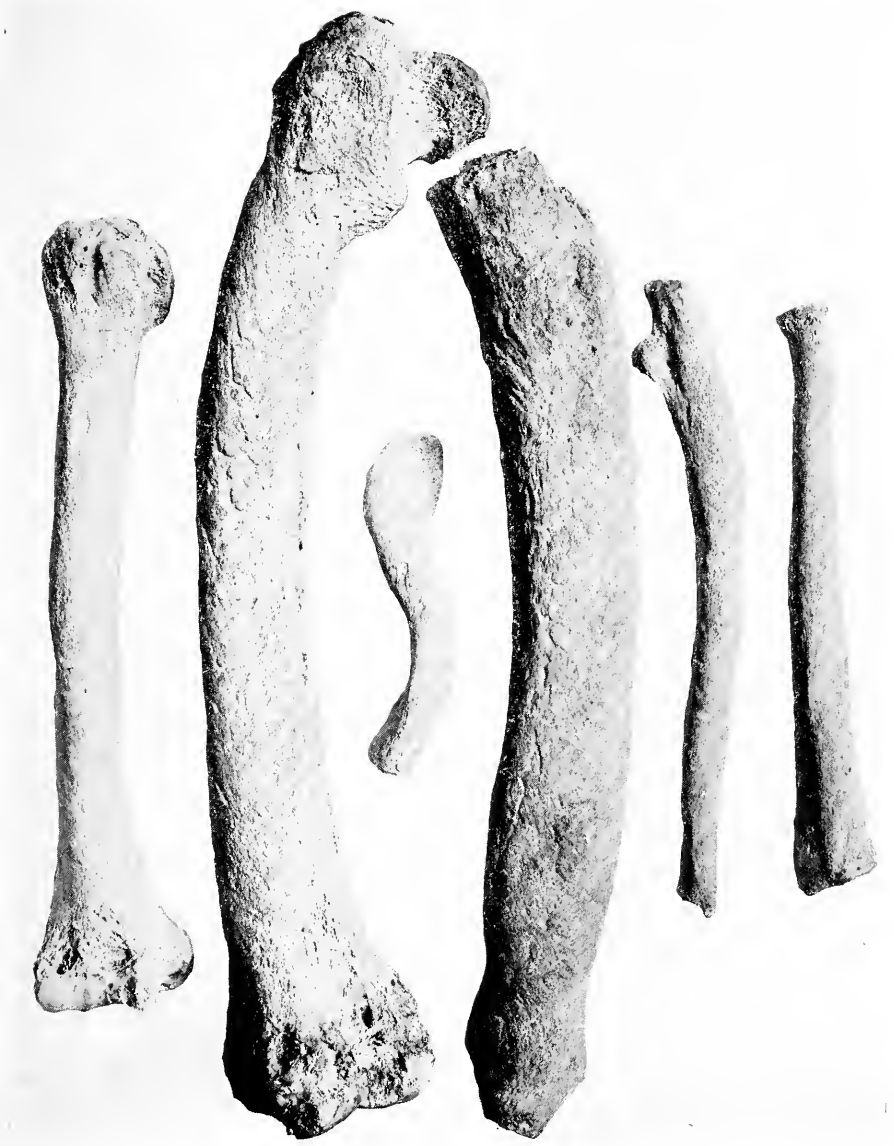

FIG. 2.—Osteitis deformans; male, age 63; humerus, femur, clavicle, tibia, ulna and radius. Observe the enormous thickening throughout, the cylindrical form, the spongy character, roughened surface and accentuation of the normal curves.

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especially the dorsal portion. Scoliosis of slight degree is likewise described. The bodies of the vertebrae appear gross, spongy and as though jammed together. The joint structures are seldom involved except late in the course of the disease when limitation of motion and slight pain may result from the deformity at the articular ends of the bones. Those most affected are the knees, hip, ankle, shoulder and elbow. Actual arthritis has been reported but probably has no direct connection with the osteitis. A localized periostitis of the tibia is not infrequent and usually results from trauma.

Cardiovascular changes of an outspoken type are so constantly associated with osteitis deformans that they should be regarded not as a complication but as an essential part of the disease. The extreme degree of atheroma of the arteries met with in this disease is seldom seen except with syphilis and occasionally in old age. So marked is the calcification in the arteries that in many of the cases the arteries of the arms and legs stand out in the X-rays as dense tortuous shadows. It has been shown that there is relatively more magnesium in the arteries than in the bones (DaCosta, Funk, Bergeim and Hawk). A majority of the cases of osteitis deformans toward the end of life develop striking clinical evidences of arteriosclerosis and the commonest causes of death in osteitis are apoplexy and cardiac failure. Mitral and aortic lesions due to sclerosis are common late in the course of the disease and at post-mortem general cardioarterial sclerotic changes have almost constantly been found.

A considerable variety of lesions particularly of the spinal cord have been described and are mentioned under etiology. As no distinct type of change existed in the autopsies recorded it seems safe to take the stand that in osteitis deformans there is no constant pathological alteration in the central nervous system. There is a reasonable basis for the opinion that the miscellaneous lesions found in the brain and cord are due to arteriosclerosis.

Chemical Changes in the Bones

Comparatively few chemical analyses of the bone in osteitis have been made. The results are variable and do not justify any very definite conclusions. Gilles de la Tourette and Magdalaine[14] and Robin[62] found a slight decrease in the organic matter with a corresponding slight increase in the total inorganic constituents. Precisely the reverse of these results were shown in the analyses of Russell (see Paget[50]), Hudelo and Heitz, Menetrier and Gauckler[45], and Moquot and Montier[47], *i.e.*, the organic matter was slightly above and the inorganic slightly below the normal. A partial explanation of these variations is to be found in the probability that the bones analyzed

represented different stages of the disease. A slight diminution in the content of lime was usually found.

Various bones from four of my cases have been carefully studied chemically with much more constant results.* With the single exception of a clavicle every bone gave an increase in the percentage of organic matter. the figures ranging from 42.60 to 48.54 per cent. Normal bone analyzed as a control showed an organic matter content of 37.83 per cent. The amount of fat present was extremely irregular but with one or two exceptions greatly increased, in the case of one bone reaching 12.05 per cent. Lime (CaO) was invariably diminished. One bone showed 41.80 per cent. of lime while the remaining seven give a range between 25.44 and 28.15 per cent. as compared with the normal of 47.42 per cent. Magnesium (MgO) was less changed though constantly below normal—minimum 0.14 per cent., maximum 0.68 per cent., normal 0.83 per cent. The chlorine, phosphorus and sulphur did not vary significantly from the normal.

Metabolism in Osteitis Deformans

DaCosta, Funk, Bergeim and Hawk[9] did complete metabolism experiments on two cases of osteitis deformans and have given an exhaustive discussion of the subject. In these experiments there was marked retention of calcium in both cases, namely, 50.3 and 18 per cent. Similar studies were made on two of my cases by Dr. Savage and a retention of calcium of 19.4 and 11.5 per cent. found. McCrudden (quoted by DaCosta, Funk, Bergeim and Hawk) found 6 per cent. retention in one case. Instead of the normal urine-feces calcium excretion ratio of 1:4.5 to 1:9 the above authors obtained ratios of 1:17 and 1:35. The ratios in my cases were normal, 1:4.16 and 1:8.35. It would therefore seem that the "phenomenon of a subnormal urinary calcium excretion" in osteitis deformans is not constant in all cases. The significance of calcium retention in this condition is not altogether clear. It is possible that further metabolism studies may show a variable retention or even a loss depending on the stage of the disease. At least a partial explanation of this retention is to be found as suggested by DaCosta, Funk, Bergeim and Hawk in the active growth of fibroosteoid tissue which is so prominent a feature of the disease. While the available analyses seem to indicate that as a rule the percentage of lime in osteitic bones is low it is important to remember that the bones are greatly enlarged indicating that even though the percentage of lime salts be subnormal the total content may

*The analyses were made by Drs. H. Carleton Smith and R. L. Emerson of the Harvard Medical School.

be normal or increased. It is possible also that the enormous degree of calcification of the arteries may account for some of the retention of calcium.

In the experiments quoted above the retention of magnesium was even greater than in the case of the calcium, *i.e.*, 35.1 and 58.7 per cent. My figures for magnesium retention were 19.9 and 10.9 per cent. and McCrudden's 20 per cent. As in the case of the calcium the normal ratio of the urine to feces excretion of magnesium was not present. In both cases they found the amount excreted in the feces greater than in the urine which is the reverse of the normal. In one of my cases this was also true but in the other the magnesium eliminated by the kidneys was nearly sixty per cent. greater than that present in the feces. The significance of the magnesium retention is probably the same as that of the calcium according to these authors.

Phosphorus likewise showed a positive balance, being respectively 28.6 and 33.3 per cent. retention in their two cases. The proportion eliminated by the kidneys was somewhat below normal. This retention of phosphorus is interpreted as resulting from new bone formation. In contrast to the above the sulphur loss was striking in one case while in the other it was practically normal.

The general interpretation of the results of the above metabolism studies as given by these writers seems reasonable. "May it not be possible that in advanced osteitis deformans the first step in the new formation of bone or osteoid tissue is the production of a highly sulphurized organic matrix, which is transformed gradually by a calcification process which is accompanied by the deposition of calcium, magnesium and phosphorus in this matrix? In the course of this calcification procedure we may suppose that a certain quota of the sulphur of the matrix is replaced by the other elements mentioned, a process which must entail the retention of calcium, magnesium and phosphorus and an accompanying increased elimination of sulphur."

Symptoms

The onset is invariably insidious, the progress of the disease being so gradual that the patient is scarcely ever conscious of its presence until many years have passed. Very commonly his first knowledge of his deformity is the result of his attention being drawn to it by his friends or family. In the advanced stages of the disease even, the patient may not have observed the striking changes in the skeleton. In the great majority of cases the first symptom is pain, usually in the skin. At the same time it may be discovered for the first time that the leg is becoming bowed. Even when the deformity is marked and general symptoms have developed the condition is often regarded merely as the infirmities of old age. Except in

those cases suffering from pain I have never known a victim of the disease to seek medical advice until very late in its course. In hospital practice the disease is almost invariably discovered in a patient under treatment for some entirely independent condition.

Pain is usually the first and frequently the most prominent symptom of the disease. It is most commonly located in the lower legs and especially over the front of one or both tibiae and is described as a dull "rheumatic" type felt deep in the bones. The pain is seldom constant and presents all possible grades from mere discomfort to actual paroxysms of a lancinating character. It is worse at the end of the day or at night and especially after long standing and unusual fatigue as in walking. The patient finds it difficult to get the leg in a comfortable position. A prone position often affords relief suggesting that hyperemia may be an important factor in causing it. Much more rarely and only late in the disease the same type of pain may be felt in the thighs, pelvis, spine and arms. Pains in the skull are rare. An intense burning and feeling of increased local temperature often accompanies the pain. Elting[11] suggests that the pain is possibly the result of distention of the periosteum. Both the pain and burning are most intense in the early stages of the disease and gradually subside after a varying number of years. A few cases are recorded where pain was absent throughout the course of the disease or appeared as a very late symptom. Joncheray[27] differentiates osteitis into the painful and painless forms, the latter seldom seen and usually in women.

Apart from pain, symptoms during the early years of the disease are not prominent. Osteitis is often seen in those of apparently robust health and it may be only after a long period of ten to fifteen years following the onset of pain that the patient feels any limitations from the process in the bones. Sooner or later, however, in a majority of instances the patient finds that he becomes easily fatigued and notes a stiffness and clumsiness in moving about. Getting up from a sitting or prone position is difficult. Muscular weakness is likewise common. When first seen the patient often presents a striking picture of premature senility. In the late stages of the disease cardiovascular symptoms are in the foreground and frequently first lead the patient to seek medical advice. Vertigo, palpitation and dyspnea are among the most common subjective symptoms. Actual cardiac decompensation with edema is not unusual. Extreme arteriosclerosis of the peripheral vessels is almost constantly found in the late stages of the disease.

One of the most constant and severe symptoms is cramps in the muscles of the lower legs. Two-thirds of my cases have given such a history. In all but one the cramps were in the calf of the leg. In one instance the paroxysms of pain were so great as to strongly suggest angina cruris. They almost invariably appear soon after the patient goes to bed.

More than half of my cases gave a history of failing vision and it seems probable that changes in the eyes are fairly constant. The marked alterations taking place in the base of the skull can hardly fail to produce some ocular lesions. Changes in the choroid and retina have been described by Vergne[72] and Glaessner[18]. Paget[52] records that of his twenty-three cases four became totally blind, one had choroiditis and three had retinal hemorrhages. Gradual impairment of hearing is the rule and total deafness often results. Apart from the influence of arteriosclerosis the cause is probably to be found in the compression of the labyrinth by the hypertrophy of the base of the skull as suggested by von Kutscha[31].

No characteristic mental impairment takes place in Paget's disease, the occasional memory weakness and confusion observed being only those incident to old age. Headache and vertigo have been mentioned in a few cases.

The muscles of the legs or arms if the bone is affected show atrophy and occasionally edema. Tenderness to pressure over the muscles may be present. The skin of the lower legs undergoes marked alterations. It is thin, often irregularly and deeply pigmented and sometimes with ulcerations or atrophic changes resembling cicatrices. Hudela and Heitz[22] report one case with melanoderma. In those cases with great enlargement of the calvarium the hair is thin or more often wanting. The sensations and reflexes are normal. The blood and the excreta present no characteristic variations from the normal.

Since the disease is essentially confined to the skeleton it is natural that the objective signs should be the most prominent. As the disease progresses the deformities become more and more pronounced and in its most advanced form afford an extraordinary picture (Fig. 3).

A study of the reported cases together with my series indicates that in all probability the disease begins in a single bone and from this as a focus the disease progresses by a gradual involvement of other or all units of the skeleton. In two instances of very advanced types which have come under my observation X-rays have shown practically the entire osseous system involved, the majority of the bones of the hands and feet alone remaining normal. The bone first attacked is with few exceptions the tibia or skull. It is claimed by several authors that the skull may be the only portion of the skeleton affected for many years and undoubtedly in a few cases this is true. The femur may be the starting point of the disease and in one case the clavicle was for some years the only bone showing changes. Wherever it begins the disease is characterized by a slow but steady progress and a tendency to an uneven bilateral and symmetrical form. One case is on record where the disease was strictly confined to one-half the skeleton (Klippel and Weil[29]). A crossed type of involvement is also occasionally observed. In the order of frequency the bones most commonly attacked

are the tibia, skull, femur, fibula, clavicle, pelvis, radius, ulna and humerus.

The head appears enormous (Fig. 3) but on close examination the enlargement is found to be largely if not wholly confined to the calvarium. It is symmetrical but with a tendency to irregularities of the surface. Especial hypertrophy of the supraorbital portion of the frontal bone and the malar processes gives to the skull a very massive appearance. The sutures are partially or completely obliterated. The head looks too large for the body. The neck is short and the head seems to rest directly on the shoulders. In the most developed cases the enormous head is thrown forward with the chin nearly touching the sternum. Motion of the head is greatly limited and the chin can be only slightly raised from the chest. In contrast the face is small. A few cases are on record in which the bones of the lower jaw were moderately hypertrophied. The marked broadening of the frontal portion of the skull gives to the face a distinct triangular outline (Marie[43]). A large majority of the males give a definite history of having year by year been obliged to increase the size of their hats and not a few have found it necessary to have their hats made to order.

The trunk in comparison with the head and prominent limbs often appears small. The thorax is compressed laterally and has a variable quadrilateral shape. Immense increase of the anteroposterior diameter accompanies the decrease in the lateral. The whole thorax is rigid and in consequence the respiration is mainly diaphragmatic in type. Hypertrophy of the ribs takes place only late in the course of the disease. The clavicles are among the bones earliest involved and are greatly thickened and misshapen. Less constantly the scapulae may show similar changes. These modifications give to the entire shoulder girdle a striking prominence. The whole spine becomes bowed with the most marked curve in the dorsal portion finally developing complete rigidity. Scoliosis is rare.

The bones of the upper extremities seldom show very noticeable alterations. Most commonly the forearm is curved in its lower half due to bowing of the ulna, the convexity being outward and backward when the hand is in the position of supination. Pronation is usually complete but supination is much restricted. Anterior bowing with thickening of the humerus is less frequent. In these bones the X-ray may very often show only a third or half of the shaft involved. Gross outward changes in the bones of the hand are never observed but roentgenograms will in almost every well marked case give evidence of the process in one or more of the carpals or metacarpals.

As a result of the anterior curve of the spine and the flexion of the trunk on the thighs the abdomen is greatly contracted from above downward. The costal border of the thorax may actually rest on the crests of the ilia. The abdomen is small, protruding and marked transversely at the level of the navel by a deep groove.

FIG. 3.—Osteitis deformans; male, age 60.

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The changes in the pelvis are among the most noticeable in the entire body. It is very broad and massive with abnormal flaring of the iliac crests. The general shape conforms more or less to the female type.

The earliest, most constant and with few exceptions the most pronounced deformities are to be found in the legs. If confined to the tibia and fibula the bowing is confined to the lower leg. When, as so often happens, the femur is also affected the curve embraces the entire leg from the hip to the ankle. Its type is always the same, namely, a broad curve with the convexity chiefly forward. No other condition except rickets in children ever gives such an extreme degree of curvature of the legs. So great may the bowing become that the legs are crossed and walking is possible only by a curious, awkward motion of extreme torsion of the body and tilting of the pelvis with each step in order that the advancing leg may clear the other. When lying down or sitting the legs are often crossed like a pair of open scissors.

On standing the knees and ankles are considerably flexed and the feet held somewhat apart strongly everted and one in advance of the other. The eversion accentuates the bowing to such an extent that the inner condyles may be widely separated. The lower legs present a most distinct and characteristic deformity, the most striking feature of which is the even, broad, forward and slightly outward curve from the knees to the ankles. The tibia has lost all its normal markings and is cylindrical in shape. Except for small irregularities the surface is generally smooth. It is in this portion of the body that the skin shows the marked changes mentioned earlier.

The deformities above mentioned give to the sufferer from osteitis deformans a posture which is peculiar and in advanced stages extremely grotesque. The enormous head which is carried forward with the chin nearly touching the sternum, the strong kyphosis of the spine, the deformed thorax, the flexion at the hip, knee and ankle joints produce the peculiar appearance which Paget likened to that of an anthropoid ape. The gait is strangely labored, slow and waddling.

X-ray Examination

X-ray examination (Fig. 4) is of the utmost importance not only as essential in showing the type of bone changes but more especially because it is the only means by which the extent to which the skeleton is invaded by the disease can be determined. In the very early stages of the process in a given bone only the proximal portion of the shaft may be involved, as is often true of the ulna or humerus and rarely of the tibia. As a rule, however, the roentgenogram reveals a diffuse change in the texture of the entire bone. All normal markings are generally lost. The marrow space is not evident after a moderately advanced stage of the process is reached. The bone is enlarged,

bowed evenly from end to end, and the outline is fairly even except for an extreme variation in the amount of lime salts near the periosteum. Legros and Léri[34] describe the outline of the bones as "soft, dim and sometimes wavy, the peripheral parts somewhat rarefied in places and hardly apparent in the X-ray." The same authors mention certain appearances of a "cotton wool-like tangled skein" structure as found only in osteitis deformans. Wollenberg[73] considers the "streaked and flakey transparency" of the bones in the X-rays as particularly characteristic of the disease. No layer of new subperiosteal bone is ever seen. In places the bone is feathery or mossy in texture while in other parts, especially near the joint ends, one sees a very coarse irregular trabecular structure. Here and there are small areas of dense bone and rarely a small area without lime representing bone cysts. Now and then the affected bone is more dense than normal throughout. The irregular double process of rarefaction and ossification shown in the roentgenograms finds its interpretation in the histological changes described under pathology.

"Mono-osteitic" Form (Schlesinger)

A considerable number of cases of osteitis deformans in which the disease process is confined to one bone have been reported but in only a few instances has the diagnosis been verified by post-mortem or X-ray examination. Commonly the deformity is found in only one lower leg but X-ray examination reveals a more or less widespread process involving many units of the skeleton. It is probable that Paget's disease frequently begins in a single bone and gradually extends to others. The characteristic course of the disease as studied in a large series of cases by means of the X-rays has convinced me that the lesions of osteitis deformans are seldom if ever limited to one bone for more than a comparatively few years. When life is sufficiently prolonged this localized process takes on a generalized form.

Hurwitz[24] (1914) collected all the cases of this limited type of osteitis which were confirmed by anatomical or radiographic examination and reported one new case, making a total of six. In the cases of Bowlby[6] and Hurwitz[24] the femur was the bone affected while in those of Schmieden[67], Katholicky[28] and Schlesinger[66] there was involvement of one tibia.

Complications

Contrary to the general opinion fractures are by no means rare and usually result from trifling causes. Nine of my cases give a history of spontaneous fracture, four of these on two different occasions. Lewald[39] reports

FIG. 4.—Osteitis deformans; male, age 63. X-rays of fibula, tibia and femur. Note the uneven surface, enlargement, exaggerated curves and double process of rarefaction and sclerosis.

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six of his fourteen cases as having spontaneous fractures. Auffret's[3] case had four fractures. Callous formation following fracture is prompt and healing normal.

Localized periostitis following trauma and nearly always of the tibia is present at some stage of the disease in a considerable percentage of cases. A slight injury to the shin often results in an exquisitely tender and painful area which persists for months. Spontaneous recovery takes place after a varying period. Joint complications of the type of true arthritis deformans or infectious arthritis have occurred so rarely with osteitis deformans that there seems no reason for accepting the view of some authors that the two conditions are related. Almost constantly, however, the patient complains of stiffness and slight pain in the joints. Objective signs are excessively rare. X-rays commonly show a slight degree of osteoarthritis. There is sufficient reason for regarding the subjective symptoms in the articulations as the result either of general senile changes or rarely of a true osteoarthritis.

The occurrence of malignant disease especially of the bones with osteitis deformans has repeatedly been emphasized. It is always a terminal complication occurring many years after the onset of the osteitis. Sarcoma is considerably more common than cancer and primary in the osseous system far more frequently than as metastasis from internal organs.

In every well marked case of this disease which has come under my observation noteworthy lesions of the cardiovascular system have been present. All have arteriosclerosis and many a very extraordinary degree of atheroma. Mitral and aortic insufficiency and myocardial disease very often appear during the last years of life. Apoplexy is one of the common causes of death.

Bronchitis, emphysema and pulmonary tuberculosis are the chief pulmonary complications but are not so frequently present as would be expected considering the deformity of the thorax.

Course and Progress

One of the most characteristic features of the disease is its chronicity. With very few exceptions the process in the bones is steadily progressive, leading to greater and greater deformity with the result that the victim sooner or later becomes in the strict sense a cripple. In a few instances where the legs have been crossed and the muscular wasting was extreme the patient has for many years been confined to bed. General disability usually goes hand in hand with the growth of the deformity, yet it would appear that the osteitis does not materially shorten life. Indeed, it is very noticeable in reviewing the statistics of the disease that the majority live to old age, death

often occurring only after the sixth and sometimes the seventh decade. The exact duration of the disease is difficult to determine since the onset is so indefinite. A course of twenty to thirty years is not rare.

An occasional exception is found to the usual progressive course of the disease when the process after a period of years seems to become quiescent, the subsequent years of life showing no evidence of increase in the deformity. The possibility of such a quiescent stage in the course of osteitis has been proved in several of my cases by repeated X-rays of the skeleton over a period of many years. Very rarely the disease may come to a standstill and then after some years again become active.

The osteitis is never the direct cause of death. Among the complications leading to a fatal termination cardiovascular disease with or without associated renal trouble is undoubtedly the most common. Next in importance is malignant disease, bone sarcoma being the most conspicuous. Less common terminal affections are pneumonia, emphysema and bronchitis, pulmonary tuberculosis and apoplexy. A few cases have died without evidence of a terminal complication and it has seemed reasonable to attribute death to a fatal cachexia.

Diagnosis

With the possible exception of the rare case of osteitis of a single bone or the unusual borderline case diagnosis is never difficult. The age, characteristic history, typical and unique type of deformities and the constant and peculiar X-ray appearances described above combine to form a definite picture which can hardly be confused with any other disease of the skeleton.

From the true diffuse hyperostosis of the skull (leontiasis ossea) osteitis is readily differentiated. In the former the process consists in an enormous hypertrophy of the entire skull and especially the bones of the face without involvement of other parts of the skeleton. The disease almost always begins in late childhood.

Rickets bears no resemblance whatsoever to osteitis except in the bowing of the legs seen in adults as a result of the disease in childhood. It is a disease of growing bones in early life and is concerned especially with the epiphyses and cartilages. In general the changes in the bones in the two conditions bear no resemblance. Likewise, the X-ray appearances of the bones in the two conditions could never be confused.

Acromegaly often shows some changes in the long bones and these together with the enlargement of the skull and kyphosis may lead to confusion of the two diseases. The process in the two conditions is entirely different in nature as well as in location. In acromegaly the soft parts are chiefly involved and the enormous enlargement of the hands, feet and face is never

present in Paget's disease. The calvarium remains unaltered and the long bones show none of the characteristics of the deformities common to osteitis. The essential osseous changes are found in the small bones of the hands and feet. Pain is absent. Acromegaly develops at a considerably earlier age.

Osteoporosis senilis has been confused with Paget's disease but without reason as there is not even a superficial similarity in the two conditions. Osteoporosis in the aged is merely "an anatomical condition and not a disease" (Pic). The process is general throughout the skeleton and is essentially an atrophy of the bone with absorption and resulting increase in its fragility. No thickening or deformity of the long bones so characteristic of osteitis deformans occurs. Pain is absent.

Secondary pulmonary hypertrophic osteoarthropathy in its final stage has in a few recorded cases shown X-ray appearances in the long bones somewhat suggestive of osteitis. While the texture of the bone and general enlargement may be comparable, there is no bowing. The massive hands and feet with extreme clubbing of the fingers and toes invariably accompany such bone changes. There is nothing simulating the grotesque deformities of Paget's disease. The presence of the primary disease in osteoarthropathy is also an important consideration.

Osteomalacia and the osteitis of Paget are both constitutional diseases affecting the long bones especially, the process being in some respects the same. As emphasized by Lunn[40], in both diseases a fatal cachexia may finally result and the same complications occur. In all other features the two diseases are quite distinct. Osteomalacia occurs chiefly in women and in the third and fourth decade. The lesions are most pronounced in the bones of the pelvis and are more strictly symmetrical. When the long bones are involved the regular curves of osteitis are absent and instead one finds angular curves resulting from fractures. Atrophy of the bone is the predominating feature. The X-ray appearances are entirely distinct. There are no cranial lesions. The general posture is unlike that of osteitis.

Cases of osteitis fibrosa osteoplastica (von Recklinghausen[59]) often bear a close resemblance to Paget's disease inasmuch as the deformities may be somewhat similar. The disease begins much earlier in life in von Recklinghausen's disease and the skull is normal. The process in the bones in both diseases shows widespread absorption of lime and the formation of new fibroosteoid bone but the pathological picture in the former is greatly modified by extensive cyst and tumor formation. Spontaneous fractures are much more frequent. Instead of the regular bowing of the bones seen in osteitis deformans, the deformities are characterized by angular curves and multiple hyperostoses and the bones are greatly enlarged by tumors.

Localized syphilitic hyperostosis of the tibia may give a superficial resemblance to osteitis deformans but otherwise the distribution and general

character of the lesions in the two diseases are quite distinct. The general objective features of osteitis deformans are never present in syphilitic affections of the bones and the X-rays are entirely unlike.

Treatment

Little can be claimed for the various methods of direct treatment which have been advocated. Drugs such as arsenic, potassium iodide and mercury are valueless. When the pain is severe preparations of salicylic acid, bromides or the analgesics so-called may be used. As the pain is usually present for many years opiates should never be given lest the patient acquire the habit. Local applications of heat often diminish the pain temporarily.

Treatment directed to the improvement of the general nutrition, rest, diet and tonics, often gives fairly satisfactory results. Hydrotherapy and light massage will sometimes materially improve the general body tone. Peckham[54] reports favorable results following the use of the actual cautery over the seat of pain and counterirritation to the lumbar spine. Orthopedic procedures for the correction of the deformities are useless.

The remarkable healing following fracture with partial correction of deformity has suggested osteotomy as a reasonable procedure. Surgical intervention of this type has been performed on three cases (Schmieden[67], Wollenberg[73] and Sonnenberg[69]). While healing has been prompt and complete the small results in the lessening of the deformity do not seem to justify the procedure.

Part II

SECONDARY HYPERTROPHIC OSTEOARTHROPATHY

Introduction

Synonyms

Clubbed fingers; Hippocratic fingers; ostéoarthropathie hypertrophiante pneumique (Marie); secundäre hyperplastisches Otitis (Arnold); osteoartropatia ipertrofica secondarie (Massalongo); toxigene Osteoperiostitis Ossificans (Sternberg); hypertrophic pulmonary osteoarthropathy; Marie's disease.

Definition

A condition, characterized by general and symmetrical clubbing of the fingers and toes, often associated with hypertrophy of the long bones of the feet and hands and less frequently with painful enlargement of the long bones of the forearms and legs. The condition is secondary to some chronic and rarely an acute disease, most commonly of the lungs.

Historical

Simple clubbing of the fingers is mentioned in some of the earliest of medical writings. Hippocrates particularly described the condition as occurring with advanced phthisis and empyema and emphasized the importance of these changes as diagnostic of purulent pleural effusion. Many of the authors following Hippocrates recognized the condition as found with many chronic diseases of the heart and lungs but always emphasized its importance as most frequently occurring with phthisis. In the nineteenth century the subject received much attention in medical literature and gradually an accurate knowledge developed as to the exact nature of the changes in the fingers and their significance. No alterations other than those in the fingers were ever mentioned by these writers until 1889 when von Bamberger[3] first described general thickening and sclerosis of the long bones, associated with clubbing of the fingers, occurring late in the course of two severe cases of bronchiectasis. In a second paper published in 1891 the same author[4] discussed at length the nature and extent of these bony changes and their relation to various diseases. The "ossifying periostitis" in the bones of the arms and legs he found with a considerable variety of diseases, bronchiectasis, empyema, phthisis and cardiac diseases.

Almost coincidently Marie[25] (1891) published a very full and accurate description of the process in the long bones and fingers, based on eight cases. Marie considered the condition always secondary to some primary disease, chiefly of the lungs, and suggested the term "osteoarthropathie hypertrophiante pneumique." Because of this careful description the name "Marie's Disease" has been frequently applied to this condition.

In more recent years the subject has been widely studied and a voluminous literature has accumulated. Papers by Walters[40] (1896), Massalongo[26] (1897), Thayer[35] (1897 and 1898), Janeway[17] (1903), Thompson[36] (1904), Wynn[41] (1904), Ebstein[8] (1906) and Alexander[2] (1906) are to be especially noted. The last mentioned author in 1906 collected from the literature seventy-seven typical cases of unquestioned secondary hypertrophic osteoarthropathy. In a careful search of the literature up to 1915 I succeeded in assembling 144 typical cases[24].

Relation of Club Fingers to Secondary Osteoarthropathy

In his second paper von Bamberger discussed the possible relationship of these two conditions and suggested that the former may be simply an early stage of the latter. He based his conclusions on the fact that three of his cases, which ante-mortem gave no evidence of changes other than the clubbed fingers, at autopsy showed periostitis of many of the long bones. The opinions of subsequent authors vary widely on this point. Many including Marie[25], Lefebvre[22], Thompson[36], Landis[21], Wynn[41], Janeway[17], Lemercier[23], Rauzier[29], Walters[40], Géraud[11], Reynaud and Audibert[31], Möbius[27], Vedel[38], Villard[39], Comby[7] and Teleky[34] regard the two as closely related if not identical. As opposed to this view Rendu and Boulloche[30], Genova[10], Labrit[20], Bezançon and de Jong[5] and others hold that there is a distinct difference between the two and that they should be regarded as independent conditions.

The evidence is entirely in favor of the former group and according to Landis may be summarized as follows: (1) both conditions are found associated with the same group of primary diseases; (2) the type of clubbing is the same, the differences described being merely the result of difference in the stage of the process; (3) clubbing of the fingers invariably occurs in secondary hypertrophic osteoarthropathy; (4) many cases which appear to be simple clubbing are shown by X-ray examination to possess alterations in the long bones precisely the same as those seen in secondary hypertrophic osteoarthropathy. In a series of thirty-nine cases of seemingly simple club fingers studied by me twelve were found by X-ray examination to have some changes in the long bones representing various stages of development. Subse-

quently Kessel[18] made a careful X-ray study of thirty-two cases of pulmonary tuberculosis of the second and third stages with varying degrees of clubbing of the fingers. In five no bony changes were found. Seventeen others were shown to have a layer of new bone beneath the periosteum of one or more of the phalanges of the hands and feet. The remaining ten cases all had unmistakable and characteristic enlargement of some of the long bones. The above evidence proves beyond a doubt that the two are but different stages of the same disease and should be considered as such clinically.

Etiology of Hypertrophic Osteoarthropathy

The great majority of cases of secondary hypertrophic osteoarthropathy are clearly secondary but a sufficient number have been reported as without a primary disease to raise the question whether the condition may not arise independently of any other disease. Most writers are in accord that the changes in the long bones and finger ends are always secondary. The literature, however, contains twenty-one cases reported as examples of secondary hypertrophic osteoarthropathy without relation to any antecedent disease. These cases were critically studied by me in 1915. Five were found to be atypical or so doubtful as to be fairly excluded as true cases of osteoarthropathy (Gerhardt[12], Gessler[13], Postmantir[28], Guérin and Etienne[14], Schmidt[32]). In three others a definite disease is mentioned as present which is among those known to cause the type of secondary changes in the bones under discussion and which it seems fair to consider as the primary condition. The history in eight others strongly suggests the presence of one of the group of primary diseases known to produce osteoarthropathy and it therefore appears reasonable to challenge them as cases of a primary type. In none of the remaining five cases was there any history of a primary disease and in each instance the author expressly states that there was none. Occurring as it does with such a variety of diseases it is to be expected that in some instances the evidence of the primary condition should be difficult to find or wanting. Some obscure cardiac or pulmonary condition, some focus of infection, syphilis or liver cirrhosis might conceivably exist without being manifest. No post-mortem examination was made in any of these five cases and without such a final test it would seem to me impossible to exclude the possibility of a primary disease. We know that in the overwhelming majority of cases Marie's disease is characteristically a secondary condition, and are justified, therefore, in demanding complete proof that any given example is primary. The five cases above mentioned while seemingly not secondary to any other disease can be regarded as only suggestive of the possibility of a primary form of hypertrophic osteoarthropathy. Until

positive evidence is forthcoming that such a primary type does exist we may assume that the condition is always secondary.

The most satisfactory grouping of the causative diseases was published by Teleky[34] in 1897 and is as follows:

1. Diseases characterized by purulent or gangrenous process, pulmonary tuberculosis, bronchiectasis, empyema, pyelonephritis, dysentery.
2. Infectious diseases and chronic intoxications, pneumonia, pleuritis, influenza, syphilis, chronic jaundice, chronic alcoholism.
3. Cardiac disease, especially the congenital forms.
4. Malignant tumors, especially of the lungs.

In 1915 I collected from the literature 139 typical cases to which were added five new observations, making a total of 144. The primary diseases in these cases were grouped as follows:

1. Diseases of the respiratory tract	112
2. Diseases of the circulatory tract	6
3. Diseases of the alimentary tract	13
4. Miscellaneous diseases	7
5. Antecedent disease unknown	6
	144

Nearly half of the above group of 144 reported cases followed either bronchiectasis or pulmonary tuberculosis. The most common causes as shown in this series of 144 cases and arranged in order of frequency are bronchiectasis, pulmonary tuberculosis, empyema, malignant disease of lungs and mediastinum, valvular heart disease, congenital heart disease, biliary cirrhosis, chronic jaundice and chronic enteritis. The above grouping of primary diseases is unquestionably very inaccurate as many of the published cases are not fully and accurately described. The recent work of Kessel[18] on the relation of hypertrophic osteoarthropathy to pulmonary tuberculosis emphasizes the importance of the latter disease as a cause of the former. There is good evidence for the assumption that osteoarthropathy is more frequently associated with pulmonary tuberculosis than any other disease.

The actual cause of the process occurring with such a wide variety of diseases has not been positively determined. The multiplicity of antecedent diseases makes it difficult to assume any single factor present in all which can lead to the characteristic secondary alterations in the skeleton. Several theories have been advanced to explain the changes found in the osseous and soft tissues. Von Bamberger suggested the theory that the drumstick fingers and proliferative periostitis are the result of toxic absorption, that is, are due to some chemical action. In support of the theory of toxic origin

von Bamberger argues that clubbing of the fingers is never seen with simple catarrhal processes in the lungs and in phthisis only in the advanced stages when purulent expectoration is present. He quotes the work of Wegner who showed experimentally that small doses of phosphorus developed a formative stimulation on cartilage and periosteum. Similar results were obtained by Gils in animals fed with arsenic. Von Bamberger attempted to produce the lesions of osteoarthropathy in rabbits by injecting bronchiectatic sputum into the rectum but his results were negative. Marie strongly advocates the toxic theory. He believes that the lesions are the "result of the production of putrid or fermented substances due to microorganisms which are absorbed into the circulation and through selective action exert an influence on certain parts of the bones and joints." It is evident from the fact that this disease occurs with certain heart lesions and other conditions where no form of suppuration exists that the toxic theory alone will not fit all cases. Von Bamberger argues that the greater part of the heart cases recorded with clubbing of the fingers and periosteal changes also have lung complications. He, however, admits that true stasis may stimulate proliferation of bone and that in some of the cardiac cases such as those of the congenital type the stasis alone may lead to the alterations in the end phalanges and long bones. There seems but little doubt that in rare cases prolonged venous congestion can produce the typical changes under discussion and even in those clearly due to toxic agents peripheral stasis may also be a factor. There is some evidence for the assumption that the action of toxic substances in the circulation predisposes the bones and joints to the alterations known to occur with congestion. In a very large proportion of cases, occurring with primary diseases of a septic type, there is deep cyanosis especially of the extremities and this peripheral hyperemia may be a factor of prime importance. The rare cases occurring with hepatic cirrhosis and malignant tumors may be explained on the basis of a true toxemia though not of bacterial origin and possibly here also stasis in the peripheral circulation plays a more or less important part. In either case the parts most affected are the distal portions of the extremities, namely, those parts most affected in osteoarthropathy.

Thorburn[37] (1893) suggests a close analogy between the bone and joint changes in chronic tuberculosis and osteoarthropathy and on this analogy bases his theory of a tuberculous origin of the disease. He regards the process as an attenuated tuberculosis of the bones and joints. Alamartine[35], in 1907, published a very comprehensive paper on the subject and finds much evidence for the tuberculosis theory. He concludes that the condition is secondary to a tuberculous infection and considers the pathological changes to be of the nature of a subacute infectious osteoarthritis. There appears to be no rational basis for such an hypothesis, however, either in the suggested analogy or in a close study of the reported cases. Clubbing of the

fingers is commonly associated with the late stages of chronic pulmonary tuberculosis but in every such case one must admit the presence of foci of toxemia and, in a majority if not in all, cyanosis is also present.

Massalongo[26] believes that hypertrophic pulmonary osteoarthropathy is not entirely dependent on diseases of the respiratory tract or on circulatory disturbances but is "the consequence of causes acting contemporaneously or alone, among which the arthritic diathesis plays the principle role" (Thayer[35]). After an examination of the cases on record it is difficult to find any basis for such an assumption.

The clubbing of the fingers occasionally seen in certain nervous diseases as well as certain clinical manifestations common to those and to osteoarthropathy has suggested a possible relationship between osteoarthropathy and diseases of the nervous system. Several authors have written in favor of such an etiologic relationship. None of the cases cited, however, have shown any lesions of the central nervous system. Alexander[2], after a critical study of all the reported cases, concludes that there is no evidence in favor of the nervous origin of osteoarthropathy.

Godlee[15] regards osteoarthropathy as due to syphilis but later writers have been unable to find sufficient evidence for such a claim. In a careful search of the literature I have found but six cases of the condition occurring with syphilis. One was associated with bronchiectasis, one with chronic bronchitis and emphysema, one with empyema and abscess of the liver, two with pulmonary tuberculosis and abscess elsewhere and one of the congenital type with jaundice.

In conclusion at least two principle causes of hypertrophic osteoarthropathy must be granted, namely, a toxemia, bacterial or otherwise, and stasis in the peripheral circulation. Either may induce the characteristic changes, the former most commonly, or both may act together.

The condition is observed most frequently in early adult and middle life. From the study of all reported cases Landis[21] found the ratio of males to females to be 8:1. There were but three negroes among 117 cases collected by Emerson[9].

Morbid Anatomy of Hypertrophic Osteoarthropathy

The numerous X-ray studies of this condition in recent years together with a considerable number of post-mortem examinations have given us a very precise conception of the essential features of the pathology. The pathological picture is an extremely irregular one varying somewhat with the nature of the primary disease and especially with the degree to which the bones and joints are affected.

End Phalanges.—It is usually stated that the typical bulbous enlarge-

ment of the terminal phalanges of the fingers and toes is entirely due to changes in the soft parts. This is undoubtedly true of the majority of the cases of club fingers without changes in the long bones although a small percentage with the X-rays show an unmistakable alteration in the first row of phalanges. It must always be borne in mind that the ungual phalanges in healthy individuals present rather extreme variations in size and shape. Among thirty-nine cases of apparently simple clubbing of the fingers studied by me, the X-rays revealed a definite proliferation of the distal phalanges in five. Three occurred with chronic pulmonary tuberculosis, one with cardiac disease and one with cardiac disease and pulmonary tuberculosis. Teleky[34], von Bamberger[4], Krüger[19], Gouldesbrough[16], Landis[21] and Reynaud and Audibert[31] describe similar changes as rarely occurring in club fingers. In the more advanced cases with changes in the long bones this hypertrophy in the terminal bones of the fingers is much more common and marked.

The alterations in the end phalanges are in the nature of an irregular mossy proliferation confined chiefly to the distal half giving to the bone a "burr-like" appearance. Rarely very long, spur-like projections are observed.

The changes in the soft parts are much more striking. The nails are greatly thickened, ridged longitudinally and curved in both directions sometimes to such a degree as to offer a very close resemblance to a parrot's beak. The nail bed is full, rounded, smooth and injected. A uniform thickening of the soft tissues gives to the part a bulbous appearance like the end of a drum-stick, hence the name so commonly applied of "drum-stick fingers." Actual edema probably does not occur, the enlargement being due to various factors including proliferation of connective and fat tissue and an injection of the capillaries about the nail bed. A slight amount of cellular infiltration has also been described. The finger ends are usually deeply cyanosed.

In some of the cases of advanced hypertrophic osteoarthropathy the whole hand is enlarged in addition to the clubbing, the fingers throughout their length being increased in size thus giving the same appearance as in gigantism.

Changes in the Long Bones.—It has been frequently stated that the process in the long bones does not begin for several years after the onset of the primary disease. This observation is doubtless correct so far as the advanced stage of the disease is concerned but it seems probable that systematic X-ray examinations of the bones of the forearms and lower legs in cases of clubbed fingers would establish the fact that changes in these parts begin much earlier. Among thirty-nine cases of club fingers studied by me, in twelve the X-rays showed characteristic subperiosteal bony proliferation of the same type and distribution as described in osteoarthropathy. In a series of thirty-two patients with advanced pulmonary tuberculosis and

clubbing of the fingers Kessel[18] found exactly the same changes in the long bones in ten. These undoubtedly represent the early stage of the typical changes seen in the well developed cases of Marie's disease. Von Bamberger mentions one case in which enlargement of the lower portion of the tibiae with pain developed within two months from the onset of the primary disease. I have recently seen a man of thirty-five who had had pneumonia nine months previously, followed by an empyema which had not been treated. Unusually well marked clubbing of the fingers was present but no evidence of changes in the long bones. X-ray examination showed a thin subperiosteal layer of new bone in the tibiae, fibulae, ulnae, radii and nearly all of the carpal and tarsal bones.

The skeletal changes in every instance probably begin in the distal third of the diaphysis of the ulna and tibia but with the advance of the process nearly the entire osseous system may become involved. Numerous X-ray studies of recent years have revealed a degree of general involvement not previously recognized. Not only are all the long bones and those of the hands and feet generally affected but also many of the flat bones as well and even the vertebrae. Changes in the inferior maxillary bone and of the skull have been recorded. A moderate degree of prognathism is described in one case.

The typical process in the bones (Figs. 5 and 6) consists primarily in a slowly progressive ossifying periostitis beginning in the distal end of the diaphysis and later involving the entire shaft. There is constantly a thickening of the periosteum which is deeply injected. The layer of new bone is very irregular in outline and appears as a very distinct sheath enveloping the original shaft. At first very thin and poor in lime salts at a later stage of the disease it becomes very dense and closely united with the cortical layer of the old bone. As a result of this proliferation the bone is increased in size in rare instances to double its normal diameter. Thayer[35] found an increase in the length of the affected bones. As the disease progresses, there develops hand in hand with the ossifying periostitis a rarefying osteitis of the old shaft which has been observed to proceed to such an extent as to entirely destroy the normal structure and appearance. This was the condition found in Case 1 of my series and the picture in the X-ray (Fig. 6) except for the absence of bowing was quite similar to that seen in osteitis deformans. At this stage the marrow space is often entirely obliterated. Suppuration never occurs. Cysts are rarely seen. Osteophytes near the costal cartilages are not uncommon.

Beyond the early stages the epiphyses are involved along with the diaphyses but the newly formed bone is of much more irregular type and less dense than the old bone. Its appearance is that of a very thick, uneven, moss-like, exuberant, new growth which stops sharply at the cartilage edge.

Alterations in the soft tissues about the diseased bone are marked and

FIG. 5.—Secondary hypertrophic osteoarthropathy. Male, age 32. X-ray of forearm showing characteristic irregular subperiosteal layer of new bone and especially the irregular and abundant proliferation of new bone about the epiphyses. Original shaft unchanged.

quite unique. The swelling is of such a high grade as to give to the forearms and legs a clumsy, cylindrical appearance. This results largely from hyperplasia of the connective tissue but edema is also a factor. Muscular atrophy of a high grade may be present especially in the hands.

Joints.—The involvement of the joints in osteoarthropathy is more constant than usually recognized, perhaps due to the fact that it is a relatively late development. In some instances the symptoms in the articulations are more prominent than those referable to the long bones and appear earlier as was true in Case 1 of my series. There is much difference of opinion, especially among early writers on this point, many asserting that no change takes place except in the periarticular tissues. Recent authors nearly all agree that at least in all well developed cases the joints themselves participate to a considerable extent in the morbid process. The joints most often involved are those adjacent to the affected bones, *i.e.*, the wrists, knees, ankles, elbows and small joints of the hands and feet. The articulations are enlarged to a varying degree principally as a result of the swelling of the periarticular tissues and the presence of fluid in the capsule. The effusion is characteristically intermittent and often considerable in amount. There is, as a rule, no local redness, heat or acute tenderness. The process is in the nature of a low grade synovitis with thickening of the capsules and a varying degree of erosion of the cartilage. In a few cases the articular ends of the bones have been found completely denuded of cartilage, though as a rule the cartilage is but little changed. Ankylosis may occur rarely as a result of the bone proliferation in the neighborhood of the articulation.

Thérèse (quoted by Thompson[36]) studied the chemistry of the new bone and found an increase in magnesium phosphate at the expense of the calcium salts as well as some increase in the organic matter.

Actual absorption of the new bone has not been observed to accompany the relief of symptoms and disappearance of swelling in the soft parts following improvement in the primary disease. Thompson[36] states that such a process does not occur. I have in two cases observed a very considerable absorption of the new bone as demonstrated by means of X-rays covering a period of several years. The endocrine glands are normal.

Symptoms of Hypertrophic Osteoarthropathy

Three clinical types of secondary hypertrophic osteoarthropathy are usually described, following Sternberg's classification: (1) clubbing of the fingers and toes without changes in the long bones. Subjective signs and symptoms are usually wanting. The condition may be secondary to any of the diseases discussed under etiology; (2) von Bamberger's type of "a higher

grade, namely, a combination of clubbing with painful thickening of the long bones especially of the forearms and lower legs." This type is secondary to the same diseases as is type 1; (3) Marie's type ("osteoarthropathie hypertrophiante") or a stage of the disease where the condition is no longer a mere incident in the course of the primary disease but by reason of the conspicuous general deformities and severe symptoms itself comes to the foreground. In this group according to Sternberg[41] the primary disease is often not prominent and may even be undetermined.

These groups in the light of our present knowledge are clearly but different stages in the development of the disease. In several cases which were under observation for some years I have watched the advance from one to another grade and any attempt at definite grouping of cases, as suggested by Sternberg[33], except for purposes of description seems to me unnecessary and confusing.

The changes in the ungual phalanges vary from the beginning thickening in the soft parts, occurring without involvement of the long bones, to the most extreme type of clubbing accompanying advanced stages of the disease. When the disease is well established the alterations in the finger ends are very striking though by reason of the absence of any subjective symptoms the patient is usually entirely unconscious of their presence. The onset of these changes is insidious. As a rule slowly progressive they may in rare instances, as with a closed empyema, develop with extraordinary rapidity and well marked clubbing be present in the course of a few weeks.

In the average case of simple clubbed fingers the deformity is sharply confined to the distal phalanx and is almost strictly symmetrical, the two hands showing equal involvement. The thumbs and forefingers are commonly the first to be attacked and hence when the condition has reached a marked stage these are apt to present a considerably greater degree of deformity. Changes in the toes accompany those in the fingers but sometimes not until the latter are fairly well marked and then the great toe is always disproportionately involved. The enlargement affects both diameters of the finger tip giving it a globular or bulbous appearance. Occasionally the increase in size is enormous, Marie recording one case which measured 10 cm. in circumference. The skin may be more or less thickened but is otherwise unchanged. More striking are the alterations in the nail. It is curved both transversely and longitudinally, thickened, and frequently shows rather marked irregularities and prominent grooves running lengthwise of the nail. Not infrequently the free end of the nail is sharply hooked over the finger end in form resembling a parrot's beak. Other nutritional disturbances, as indicated by increased brittleness, are also met with. In well developed cases the greatest prominence of the nail is at about its central portion. Varying degrees of cyanosis of the nail are the rule. The

affected nails are said to grow more rapidly than normal. The nail bed is raised, abnormally smooth and deeply injected. Pressure over the root of the nail gives a sensation of fluctuation as though the root were resting on a fluid cushion. At this stage muscular atrophy in the fingers often accentuates the clubbing.

With the approach of a later stage of the disease and accompanying the process in the long bones the whole hand becomes altered. It appears gigantic, crude and "paw-like." The fingers look puffy and are sometimes moderately spindle shaped. They seem stiff, are handled clumsily, muscular power is greatly diminished and the hand cannot be closed completely. The general appearances in the hands suggest the presence of arthritis in the joints of the fingers and metacarpophalangeal joints, but aside from a moderate thickening of the periarticular tissues and slight stiffness or very moderate dull pain there is no real evidence of an actual arthritis. Quite analogous changes occur in the feet but are less evident in the toes than in the tarsus and ankle. Von Bamberger has aptly suggested the term "elephant foot" for the most extreme type of deformity in the foot. The hands and feet are moist from excessive sweating.

When the long bones are involved the clinical picture becomes a more complicated one and the symptoms are no longer solely objective. Pain is the most prominent and constant symptom and generally develops with the appearance of swelling in the legs and forearms to which region it is almost invariably confined. It is variously described by the sufferers as a mere discomfort, a burning or prickly sensation, or, more commonly, as a deep, dull ache in the bones which for a considerable time, at least, increases in severity as the disease advances. In some of the cases of long standing the pain may disappear entirely. It is apt to be intermittent occurring for short intervals or only at night or in the legs after long standing. More rarely the pain is constant and agonizing as indicated by a few reported cases. I have only once met such an extreme case and then the pain and tenderness were of the exquisite type so common to rheumatic fever. Cold accentuates and warmth relieves the pain. The patient usually finds that the pain in the arms and legs as well as the swelling is worse during the periods when the primary disease is most active, as in the case of bronchiectasis or lung abscess, when the sputum is most abundant and purulent. In other words, the symptoms of the secondary disease quite definitely run a course parallel to that of the underlying disease. Sensitiveness over the enlarged bones always accompanies the pain.

The evidence of bone involvement begins in the distal third of the forearms and lower legs and it is in these regions that the process reaches its most extreme degree. When fully established the whole forearm and lower leg are cylindrically enlarged and of about the same diameter throughout

Fig. 7). A moderate degree of edema may be present and in the most acute cases some local increase in temperature is associated with the pain and tenderness. In its extreme development, that is, when the osseous system is generally affected, the disease presents a very unusual picture. General and extreme emaciation is present, likewise a considerable degree of anemia. The patient is weak, holds himself stiffly and moves about clumsily as a result of stiffness in the spine and joints. Kyphosis of varying degrees may exist.

Fig. 7.—Secondary hypertrophic osteoarthropathy. Male, age 30. Observe the clubbing of the fingers and toes and the marked cylindrical enlargement of the lower legs and forearms.

A more or less general involvement of the joints, similar to arthritis in the hands, accompanies the late stages of the disease. Those joints adjacent to the most marked osseous changes are the ones showing the most signs, *i.e.*, the wrists and ankles. The principal and the first complaint may be of pain and stiffness in the articulations, usually the wrists and ankles. Actual inflammation of the joints is seen in exceptional cases. The acute symptoms in the joints are invariably associated with an elevation of temperature which subsides coincidently with the disappearance of the symptoms. Thompson[36] observed enlargement of the glands in the axilla and groin associated with the acute stage of the process in the wrist and joints of the lower extremity. He regards the process in the joints in all cases as unquestionably inflammatory in type. Subluxation or other forms of dislocation are unknown, although a slight degree of hyperextension is mentioned. There is no grating in the affected joints.

Mention has been made of the parallelism between the symptoms of the osteoarthropathy and the course of the primary disease. Two cases under my observation have had acute exacerbations of a very noteworthy type

which did not seem dependent on an exacerbation in the primary condition. There was a sudden onset of intense pain with the development of swelling and very acute sensitiveness over the bones, high fever and great prostration. This acute stage lasted for two or three weeks, the symptoms then gradually subsiding. These acute attacks bear a striking resemblance to the course of rheumatic fever.

Painful swelling of the breast similar to that seen in males at the time of puberty has been noted by von Bamberger[2]. Brooks[41] cites several cases with bulbous enlargement of the nose and thickening of the malar region. Kessel[18] also observed these in six of his ten cases. Skin lesions in my experience are rare but Alexander[2] mentions ichthyosis, eczema, erythema, pigmentation and rapid growth of hair on the affected parts as occasionally occurring. Organic disturbances except as associated with the primary disease are unknown. There is no reaction of degeneration in the muscles, no change in the reflexes and no sensory disturbances.

The course of the disease is, like its clinical types, extremely varied and probably depends entirely on the course of the primary disease. All symptoms and signs may disappear if the lesions in the lungs or elsewhere producing them are cured. Rarely the disease follows a chronic progressive course without discoverable activity in the antecedent disease. At times after a period of activity of many months or a few years it subsides into a quiescent state. Ordinarily the course throughout is with periods of alternating activity and inactivity. The duration is often many years since the disease being a secondary condition has no direct influence on the general health.

Diagnosis of Hypertrophic Osteoarthropathy

Diagnosis presents no difficulties since the well marked lesions of osteoarthropathy can hardly be confused with any other disease. But few diseases present objective signs which are so absolutely unique and characteristic. Clubbing of the fingers should always lead to an examination of the bones of the hands and feet as well as those of the forearms and legs. It is only by this means that it is possible to detect the early stages of the periosteal proliferation so characteristic of the disease. The fairly regular sheath of new bone is met with in no other condition. The combination of the clubbed fingers and painful thickening of the long bones showing the peculiar subperiosteal layer of bone in the X-rays and, occurring with some diseases of the lungs and rarely with other conditions, is pathognomonic of the disease.

The resemblance of this condition to acromegaly is only a superficial one. Acromegaly is a primary disease. The peculiar changes in the face are

wanting in osteoarthropathy. The hands may be enlarged and clumsy in osteoarthropathy but do not simulate the appearances seen in acromegaly. Symptoms referable to the central nervous system are never present in osteoarthropathy. Clubbing is unknown in the latter and the nails are small. The alterations in the long bones as seen in the X-rays are seldom pronounced and consist merely in an irregularity of outline especially in the epiphysis and an accentuation of the prominences marking the muscle and tendon attachments.

In occasional cases where the joint symptoms are most pronounced the osteoarthropathy may be mistaken for chronic arthritis. The joints, however, very seldom show any outspoken evidences of inflammation and the deformities so common to chronic arthritis are lacking. Clubbing of the fingers and thickening of the long bones are never seen in arthritis.

Heberden's nodes likewise should never be confused with osteoarthropathy. In this condition clubbing is wanting and the enlargement is not in the distal portion of the end phalanx but about the joint which is deformed. These nodes are due to an osteoarthritis of the joint with hypertrophy of the bone which takes the form of osteophytic outgrowths on the dorsal surface at the edge of the joint cartilage. The process is observed only in old people and is a primary affection.

Treatment

No form of therapy has any direct effect on the condition itself, though, as mentioned above, relief of the underlying disease often leads to prompt improvement in the bones and finger ends. For the pain hyperemia treatment by means of the application of heat in some form or counterirritation is indicated. Analgesics may even be indicated in the rare cases with pain of an intense type. The general treatment is the same as that for any chronic debilitating disease.

Part III

OSTITIS FIBROSA CYSTICA

Introduction

Definition.—A rare chronic degenerative disease of the bones beginning in late childhood and characterized by extreme metaplasia of osseous into fibrous tissue with the formation of benign giant-celled tumors and cysts leading to marked deformities and fractures.

Synonyms.—Allgemeine Hyperostose des Skelettes mit Cystenbildung (Virchow); Osteomalacia mit Cystenbildung (Hirschberg); tumorbildende Ostitis deformans (Sternberg); Ostitis fibrosa osteoplastica (von Recklinghausen); Ostitis fibroplastica (Franke); Osteodystrophia juvenilis cystica (von Mikulicz); Chronic osteomyelitis fibrosa cystica (Bloodgood); von Recklinghausen's disease.

This disease is one of the last to be separated from the miscellaneous and confused group of bone conditions. Credit for its recognition is due to Hirschberg[13] who, in 1889, published under the title "Zur Kentniss der Osteomalacie und Ostitis Molacissans" a very exact description of the pathology of specimens at the City Hospital in Dresden previously considered as multiple cystic sarcoma. He mentions as cardinal features the long course, weakness of bones, multiple fractures and cyst formation. As to the nature of the process he concludes that it should be regarded as a late stage of "osteomalacia with cyst formation, multiple fractures and secondary development of sarcoma."

Von Recklinghausen[25], however, in 1891, first definitely separated ostitis fibrosa from other bone diseases with degeneration and weakness of osseous tissue. Since then the disease has been studied by many investigators and a relatively larger number of cases have been described. Bloodgood[2], in 1910, collected sixty-nine typical cases.

Clinical Types of Ostitis Fibrosa Cystica

Two distinct clinical types are recognized, the localized form in which the fibrosis and cyst formation are confined to a single bone and the rarer general form in which multiple bones are involved (Fig. 8). Ringel[27] states that there are only thirty cases of this latter type in the literature.

The bone cysts which are constantly found in ostitis fibrosa also develop secondary to many other primary pathological conditions. Silver[29] groups

them as follows: (1) those from softening in malignant tumors; (2) those due to bacterial infections (bone abscess); (3) those due to parasites (cysticercus, echinococcus); (4) those with rare bone diseases (arthritis deformans, senile osteoporosis, osteomalacia); (5) those as minor symptoms of osteitis deformans, or general symptoms of ostitis fibrosa; (6) those with callus; (7) those in Barlow's disease.

FIG. 8.—Ostitis fibrosa cystica. Skeleton of woman of 40. (v. Recklinghausen.)

ETIOLOGY

The cause of the disease is still undetermined. Although benign cysts are common in the early years of life true ostitis fibrosa rarely develops before ten or after twenty. Von Mikulicz[20], König[15] and Bloodgood[2] emphasize especially the fact that the vast majority of cases occur before the twentieth year, *i.e.*, during the time of life when bone growth is active. The last mentioned author found but five cases among the sixty-nine collected who were over twenty at the time of onset. Frangenheim[7], however, calls attention to the fact that although the condition is rarely seen until after the tenth year the history will often give evidence that the process existed much earlier but was unobserved. His figures of published cases indicate that fifty to sixty per cent. are first seen during the second decade. Clearly the disease is of slow development and its course in the average case covers a period of years. The ratio of females to males is 48:39 (Bloodgood).

The disease has been explained on the basis of various etiologic factors, heredity, hereditary syphilis, toxic conditions, trauma, perverted in-

ternal secretions, inflammatory nervous diseases and rheumatism. Rehn[26] holds that the disease results from bone dystrophy, *i.e.*, an overdevelopment of a physiological process as in callus, rickets, osteomalacia, sarcoma and senile osteoporosis. Our present knowledge of the disease will not permit any definite opinion as to the cause, but it seems most reasonable to regard the disease as such a dystrophy of growing bones in which a chronic inflammation plays a prominent part (von Mikulicz[20, 21], Tietza[30], Bloodgood[2], Murphy[23]). As a result of a careful study of all reported cases Bloodgood says, "I agree with all the more recent investigators that the disease is an inflammatory one."

There seems to be abundant evidence that trauma and probably also the resulting hemorrhage plays some and perhaps an important part in the formation of the cysts (von Recklinghausen[25], Franke[8], Monckeberg[22], Bloodgood[2], von Mikulicz[21], Hartmann[11]). Bolognesi[3] conducted a long series of experiments on rabbits in an attempt to produce bone cysts by various forms of trauma. The author interprets his negative results as a refutation of the theories of a traumatic or infectious origin of cysts.

Pathology

The main features of the pathological changes in the bones are: (1) a general and diffuse degeneration and absorption of the old bone; (2) a curious growth of connective tissue; (3) development of benign spindle-celled sarcomas; (4) formation of cysts; and (5) occurrence of spontaneous fractures (Hirschberg[13], von Recklinghausen[25], Monckeberg[22], Pfeiffer[24], Rehn[26], Gaugele[10], Tietza[30], Füjii[9], Hartmann[11], Lissauer[18], Brunn[6], Matsouka[19], Bolognesi[3], Frangenheim[7], Saurborn[28]).

The bones involved in the localized form of ostitis fibrosa are the long ones. Most commonly the humerus, femur and tibia are the seat of the lesions. In the generalized form practically the entire skeleton may participate. The skull, which usually escapes, in one of von Recklinghausen's cases[25] (Case 5) showed an irregular and unsymmetrical involvement. In consequence of the tumor formation and fractures the individual bones in both forms are greatly altered in size and shape (Figs. 9 and 10). The process is confined to a portion of the bone only, usually the proximal end. The bowing in the upper and lower extremities is of a very angular and irregular kind.

The very complex, interosseous lesions found are confusing, and the relationship and sequence of the various changes are not fully understood. The earliest process is probably a degeneration of bone of high degree due to lacunar absorption beginning in the metaphesis. This bone destruction is

accompanied by an irregular new formation of fibrous tissue. The bone presents a most unusual picture. On section it shows a varied mixture of remains of old bone, widely scattered connective tissue islands, small remains of cartilage, deep injection of the tissue or even hemorrhages and, finally, cysts. The marrow shows clearly the evidence of a fibrous metaplasia of all grades. In appearance it may even suggest fibroma. In general the normal compact substance of the diaphysis is replaced by a fine or coarse connective tissue rich in fibroblasts. The epiphysis is much less altered. It is evident from the character of the bone that transudates and hemorrhage play a prominent part. The periphery of the bone shows equally marked degenerative changes. Instead of the dense compact bone one finds an extremely irregular structure with many small cavities, scattered trabeculae, Volkman's perforating canals, Howship's lacunae and everywhere fibroosteoid tissue. In places the cortex is only the thickness of parchment.

The periosteum does not appear in any way to react to the disease until fracture occurs when it participates in the healing process by callus formation. As a whole the osseous tissue contains less lime than normal and in consequence the bone can be readily bent or depressed. A "rubbery flexibility" has been described. The metaplasia into fibrous tissue is often so extreme that small or large tumors are found. Because of the abundant giant cells present in these tumors they are called "giant-celled sarcomas." They are, however, benign.

The cysts (Fig. 10) are usually found in the shaft of the long bones near the epiphyseal end though very rarely in the skull and flat bones also. The most characteristic form is the small, smooth-walled, rounded type. In the cysts of long standing the bony wall becomes extremely thin or if peripherally placed may have only a wall of periosteum. There is no true epithelial lining though a few possess an indefinite covering of connective tissue cells. A few instances of multiple cysts have been recorded. The contents are whitish to a deep brown, consisting of gelatinous, cheesy or serous material. Actual hemorrhagic fluid is never found (Bloodgood).

The origin of the cysts was attributed by Virchow[31] to the breaking down of remains of cartilage either new formed or from remnants of the epiphyseal cartilage. Von Recklinghausen's theory that they arise from degeneration and softening of the fibrous tumors is generally accepted (von Recklinghausen[25], König[15], Heineke[12], Monckeberg[22], Lissauer[18], Tietza[30], Matsouka[19], Bloodgood[2], Füjii[9]). Evidence strongly points to trauma and hemorrhage as important but not the only factors in causing cysts (Franke[8], von Mikulicz[20, 21], Konjetzuy[16], Jenckel[14], Landon[17], Bolognesi[3]). On the basis of this conception Frangenheim considers the cysts as the last stage of

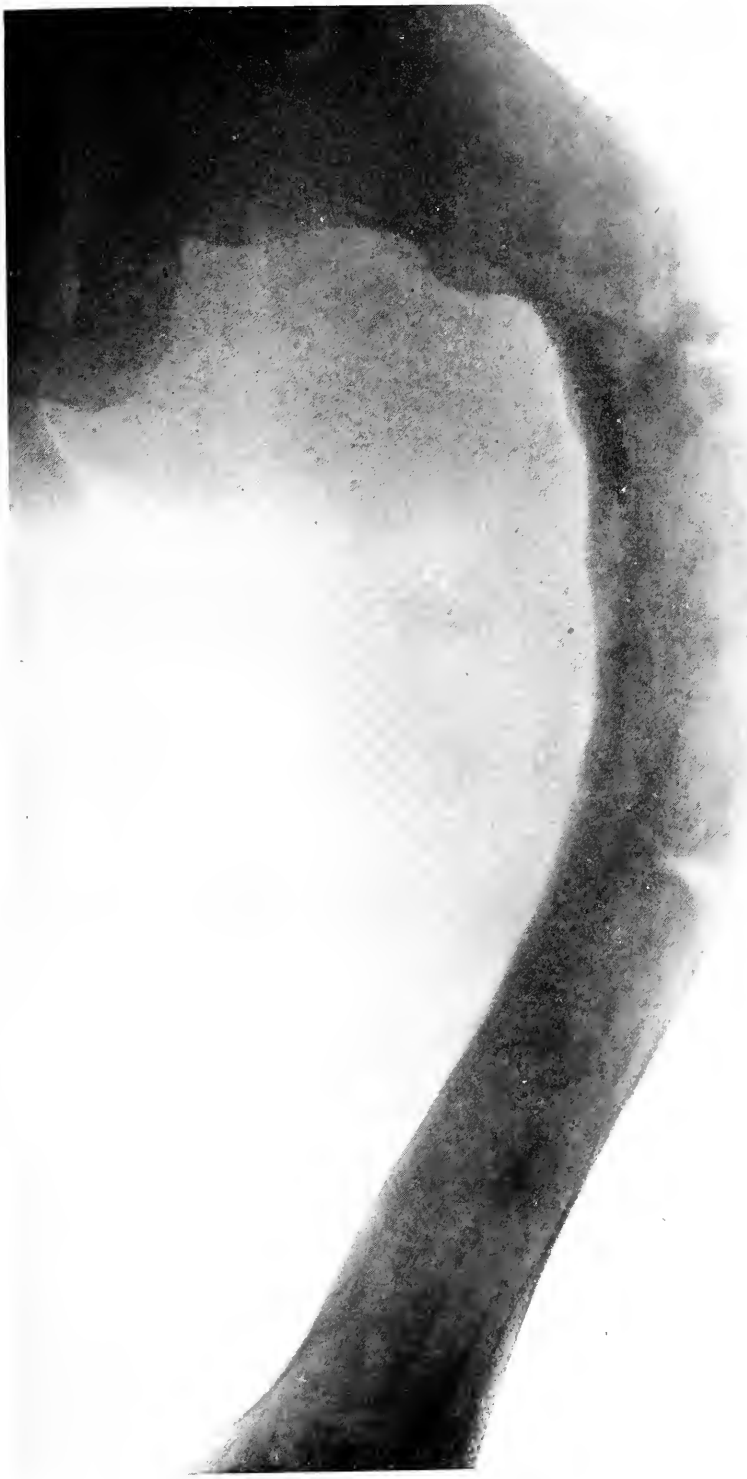

FIG. 9.—Ostitis fibrosa cystica. Male, age 18 years. X-ray of left femur showing uniform thickening, bowing, fractures and striking alterations in bone structure. (Case of Dr. R. W. Lovett.)

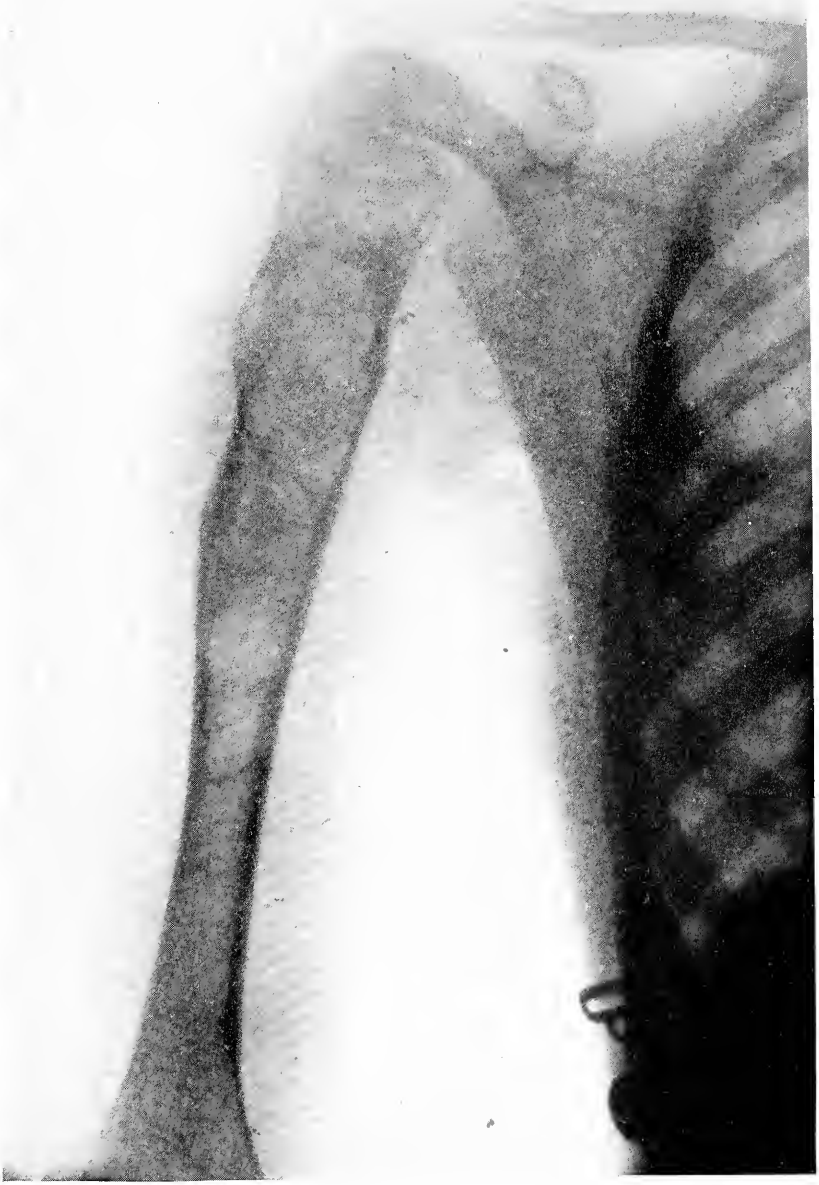

FIG. 10.—Ostitis fibrosa cystica. Female, age 8 years. X-ray of right humerus showing in upper half enormous thickening, irregular outline and general thinning of bone with multiple cysts. (Case of Dr. A. W. George.)

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the process in ostitis fibrosa. Von Mikulicz[20] believes that the development of cysts is a matter of years.

Spontaneous fractures or fractures resulting from insignificant trauma inevitably occur as a result of the weakening of the bone (Fig. 9). Bloodgood[2] found only a single case of ostitis fibrosa where fracture was not present. The fracture is very frequently multiple. A rich callus formation is always to be expected and prompt healing results. Von Bergmann[1] considers that the breaking of the cyst wall with fracture acts as a strong stimulant to the growth of new bone.

Symptoms and Course

In common with many other bone diseases characteristic symptoms are not prominent. Symptoms usually appear late in its course or rarely are wanting throughout and are in general those common to intramedullary disease. It may safely be assumed that the bone has been the seat of disease for at least several months if not years prior to the advent of symptoms.

A trifling injury may produce a fracture and first call attention to the process in the bone. Von Brunn[5] finds this one of the earliest symptoms. Spontaneous fracture has occurred in thirty-five of the recorded cases according to Silver[29]. It is most frequently seen when the humerus or femur is the seat of the disease. A few examples of incomplete fracture are recorded.

Pain was the first symptom in twenty-five per cent. of the cases collected by Silver[29]. It is variously described as "rheumatic," "dull," or "aching," and less often as mere lameness or stiffness. This symptom is never distressing. Rest affords relief. Tenderness may be present over the cyst. The joints are unaffected.

As the disease progresses deformity appears. The bone is swollen in the region of the cyst and occasionally reaches enormous size (Figs. 9 and 10). Bowing of a more or less angular, irregular type and confined to a fraction of the shaft is often observed. Von Brunn[6] reports in a girl of ten an extraordinary case of ostitis fibrosa of both femora with multiple fractures and resulting coxa vera of such marked degree that the legs were crossed. Shortening may result. When several of the long bones are involved more general deformity develops (Fig. 3). With marked changes in the bone atrophy of the leg or arm has been seen. Bloodgood[2] mentions a limp as one of the rare symptoms. A moderate degree of disability may result from the deformities.

Metastases from the tumors have never occurred. Complications are not described. The course is chronic and marked by the occurrence of one or

more fractures with increasing deformity. Bloodgood gives a duration of eighteen months to eighteen years.

X-rays are of the first importance in this disease as a differential diagnosis is practically impossible without them. The cyst cavity is clearly shown usually as a single smooth, rounded, transparent area which cannot readily be confused with any other condition. The medullary cavity of the bone is partially or completely obliterated and the shaft shows typical atrophy with scattered coarse trabeculae running longitudinally. The epiphysis except in the most advanced cases is normal. The outline of the bone is regular and the periosteum continuous.

Diagnosis

Ostitis fibrosa may easily be confused with osteomalacia, osteitis deformans, tuberculosis, syphilis, bone abscess and certain types of new growths of bone, particularly the osteosarcomas, and a definite diagnosis in the early stages is sometimes impossible. The following characteristic features of the disease are important to bear in mind in differentiating the condition from the above. The disease almost invariably appears between the tenth and twentieth year. Symptoms are in the background. A history of slight trauma with resulting fracture is usually present. The angular, localized deformity of the bones with irregular enlargement usually of the proximal one-third and the absence of local symptoms of inflammation are seldom seen in any other disease. The disease affects almost exclusively the femur, humerus and tibia and even in the generalized form these are the bones showing the most marked and characteristic alterations in size and shape. Spontaneous fractures are particularly prominent. A long course with increasing deformity but without the appearance of severe symptoms is the rule. The radiographic appearances are unique.

Osteomalacia occurs almost exclusively in females and seldom until after twenty. Pain and tenderness over the bones are more prominent symptoms. The bones most constantly affected are those of the pelvis. The deformity is more general and extreme. Disturbance of gait and finally a condition of almost complete helplessness develop. Cysts do occur but with less constancy. The histological picture in the two diseases is in most features entirely different. Roentgenograms show quite distinct differences in the two conditions.

Osteitis deformans (see Part 1 of this Chapter).

Tuberculosis of the bone is confined to the epiphysis and the local signs are usually quite different. The roentgenographic examination readily excludes tuberculosis.

Syphilis localized in one of the long bones may strongly suggest ostitis fibrosa but the clinical picture, the X-ray appearances and the Wassermann test should serve to prevent any confusion of the two conditions.

Bone abscess, as in the case of other inflammatory bone processes, gives local signs of secondary reactions. The deformity of ostitis fibrosa is never simulated by abscess. The X-rays show in the medulla of the shaft a central area of softening with irregular walls, often with sequestrum and marked bone proliferation, especially peripherally, beneath the periosteum.

Sarcoma of the bone is the variety of malignant tumor most commonly confused with ostitis fibrosa. The disease nearly always remains confined to a single bone. Both the local and general reaction is more severe. In the X-rays the process is more irregular and does not show the characteristic appearances seen in ostitis fibrosa and described above. The cortex is broken through with the result that the surface is roughened.

Treatment

Treatment is primarily surgical and the results of operative intervention have been, generally speaking, good. Fractures should be treated as any other fractures. Repair is practically always prompt and complete. Among the methods of operative treatment advised are aspiration, curettage, osteotomy and excision in the case of the small bones. The operation of choice is to open the cyst and curette out the diseased bone. Excision is rarely indicated.

Immobilization of the affected part is occasionally necessary. Prophylaxis in the form of protection to the region involved and the regulation of the activities of the patient to the end that dangers of fracture from trauma be minimized is important. General hygienic-dietetic measures should not be neglected.

Bookman[4] quotes a case showing marked calcium retention with evidence of general improvement following the administration of calcium lactate and suggests that the value of calcium therapy should be tested.

Part IV

OSTEOPSATHYROSIS (OSTEOGENESIS IMPERFECTA)

Introduction

Definition.—Osteopsathyrosis is a rare condition, probably congenital in origin, appearing most commonly in fetal life, somewhat less frequently in infancy and very rarely in childhood and adult life. The disease primarily affects the bony tissues and is characterized pathologically by a deficient and abnormal bone development and clinically by multiple spontaneous fractures of the bones of the arms, legs and ribs.

Synonyms.—Osteopsathyrosis idiopathica (von Lobstein, 1833); osteogenesis imperfecta (Volrik, 1845); fetal rickets; rachitis annularis; osteoporosis foetalis (Kundrat); osteomalacia congenita (Jurgen, Marchand); dysplasia periostalis foetalis (Klebs); fragilitas ossium (Klebs); periostale dystrophia (Porak and Durante); periostale dysplasie (Durant); periostale aplasie (S. Muller); pseudochondritis (Schildowsky); myeloplastische Malazie (von Recklinghausen); ostitis parenchymatosa chronica (Schmidt); osteogenesis imperfecta, congenita and tarda (Looser); Lobstein's disease.

This imposing array of terms gives evidence of the confusion which has existed in the past regarding the nature of this disease and its relation to other bone affections occurring in fetal and early life. In the earlier writings many cases of this condition were undoubtedly described as a congenital form of osteomalacia, or, more commonly, as fetal rickets. All modern authors are agreed that osteopsathyrosis is in no way even indirectly related to either rickets or osteomalacia.

The first case of osteopsathyrosis was published by Amand in 1716 as "intrauterine fractures without preceding trauma" (quoted by Gurlt). Von Lobstein[17] in 1833 gave the first accurate clinical description of the cases occurring in infants and children with general fragility of the bones. A detailed description of the alterations in the form of the bones as well as in their structure is given. He explains the pathogenesis on the basis of an "inertia of function." Von Lobstein was also the first to recognize the influence of heredity in this condition. On the basis of the changes found in the bones this author gave to the condition the name "osteopsathyrosis idiopathica" meaning an idiopathic fragility of the bones. In 1845 Vrolik[31] suggested the name osteogenesis imperfecta as best describing the pathological conditions found and it is under this designation that many of the cases have been reported.

The most exhaustive discussion of the subject among the earlier writers

is found in Gurlt's Handbuch[12], published in 1862. The author gives a careful analysis of all recorded cases and makes important contributions to the nature of the disease and its relation to other diseases of fetal and early life affecting the bones. From the cases collected he assembles conclusive evidence of the hereditary factors in etiology. Since 1862 the disease has been the subject of many careful studies and numerous noteworthy articles have appeared. Griffith[11] in 1897 succeeded in collecting 67 cases from the literature and in 1914 Ostheimer[24] added 126 subsequently published, making a total of 193. The disease is much more rarely seen, however, than this relatively large number of cases would seem to indicate. Birnbaum[4] among 45,000 births in the Göttingen Frauenklinik found but a single instance of osteopsathyrosis.

Increased fragility of the bones of varying but usually moderate degree is seen in symptomatic or secondary form with a considerable variety of diseases, old age (senile osteoporosis), bone diseases (osteitis, osteomalacia, osteomyelitis, rickets, hereditary syphilis, tuberculosis, malignant diseases, echinococcus and other cysts), trophic neurologic diseases (locomotor ataxia, poliomyelitis, syringomyelia), mental diseases, scurvy and phosphorus poisoning. Brittleness when it occurs with any of the above conditions is readily explained by obvious alterations in the bone as a result of the primary diseases.

Types of Diseases

Three types of the disease have been described: (1) the fetal form (osteogenesis imperfecta or fetal osteopsathyrosis) (Fig. 11) in which the fractures are chiefly intrauterine, the child often being premature and either stillborn or not long surviving after birth; (2) the infantile form (infantile or idiopathic osteopsathyrosis) appearing in children who show no fractures until a year or two after birth; (3) the adult form (idiopathic osteopsathyrosis) met with as an idiopathic fragility of the bones after childhood (Fig. 12).

Bamberg and Huldschinsky[2] found the ratio of the number of the fetal type to the later form to be approximately 1:3. Looser[18] separates the cases into two general groups, namely, osteogenesis imperfecta congenita and tarda. Any such division, however, is of value only for purposes of description as nearly all modern writers are agreed that there is no essential difference in the disease as seen at different ages (Schuchardt[26], Nathan[22], Ziegler[32], Looser[18], Frangenheim[9], Sumita[30], von Bamberg and Huldschinsky[2], Schwarz and Bass[27], Kienböck[16], Mixsell[21], Hess[14] and others). Both the clinical picture and the pathological anatomy in the congenital and later forms are identical except for such slight variations as can be

explained on the basis of the difference in the stage of development. Looser[18] and Kienböck[16] especially emphasize the fact that all possible transitional cases between the two have been observed. Hess[14] suggests that the osteopsathyrosis appearing in later years is but a latent form of the usual congenital type as in the case of hereditary syphilis where

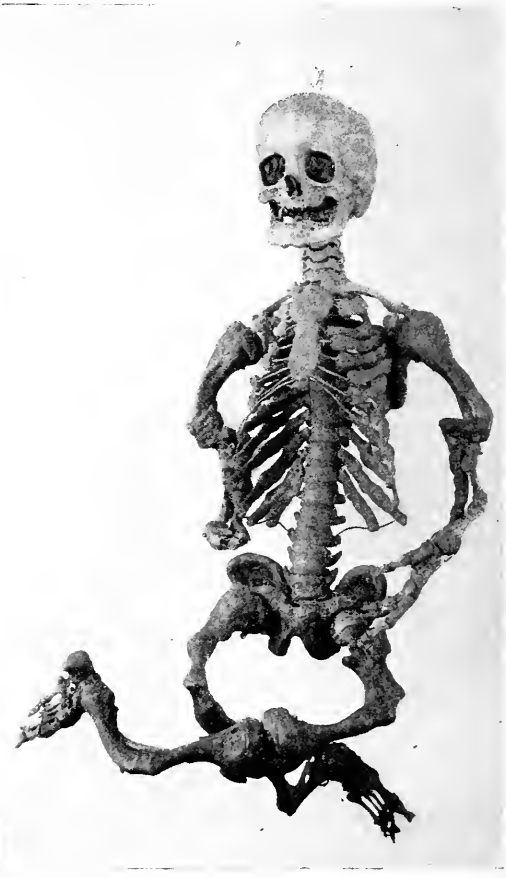

FIG. 11 FIG. 12

FIG. 11.—Osteopsathyrosis congenita. Skeleton of seven months fetus. Note the innumerable fractures. (Warren Museum, Harvard Medical School.)

FIG. 12.—Osteopsathyrosis. Adult form. Skeleton of woman of 21. Note multiple fractures and resulting deformities. (Warren Museum, Harvard Medical School.)

the evidences of the disease develop at birth or only after a longer or shorter latent period. Looser[18] believes that the osteopsathyrosis of adults is the result of congenital bone changes.

Etiology

The actual cause is undetermined. The sexes are about evenly divided, the males according to Ostheimer[24] comprising fifty-three per cent. of the reported cases. Heredity seems to be an etiologic factor of some importance. Both von Lobstein[17] (1834) and Gurlt[12] (1862) emphasized the fact that in this form of bone fragility there is often striking evidence of hereditary influence. Since the time of these early writers much evidence has accumulated to prove that a family tendency in osteopsathyrosis plays a role of some importance although it in no way actually explains the disease. Griffith[11] found that eighteen among sixty-seven collected cases gave a history strongly suggesting family predisposition. Transmission is usually through the male side. Gurlt presents evidence that the tendency may rarely be passed on to the male members through unaffected females.

No constant changes in the central nervous system or endocrine glands have been found to explain the changes in the bones. Syphilis is not a factor. Kienböck[16] expresses the opinion that in the idiopathic form of osteopsathyrosis the nature of the changes in the skeleton suggests that the disease is not a primary bone affection but one of some central organ (osteotrophic organ) which furnishes some substance necessary for the normal formation and nutrition of the bones. Biggs[3] regards the disease as probably of nervous origin and therefore to be considered a neuropathic affection. The opinion of Harbitz[13] that the disease must be considered as due to some disturbance of nutrition affecting the entire bone system during fetal life seems the most reasonable one.

Pathology

In this disease the pathology is essentially concerned with the skeleton which to a varying degree is affected throughout (Figs. 11 and 12). The bones both in their outward form and abnormal internal structure are entirely unlike those of any of the other so-called bone diseases. Though presenting a great variety of changes, especially at different ages, a fairly definite and characteristic picture may be described. The bones showing the most marked alterations are those of the extremities and ribs.

As a rule the bones develop normally in length but often become shortened in consequence of bowing and fractures. They appear thin and delicate. The diaphysis may be straight and cylindrical or flattened and greatly deformed. Actual bowing independent of fractures does occasion-

ally occur (Kienböck). The most characteristic outward feature of the long bones is the angular deformities. The diaphysis is soft and brittle but almost never shows any increased flexibility. No epiphyseal enlargement is present.

The head is usually described as of normal size and shape. Frangenheim[9] speaks of a very rare hydrocephalic type. The cranium (Fig. 11) shows a more or less complete absence of calcification, in extreme cases appearing only as a membranous sac (calvaria membranacea). In other cases the calvarium is made up of a "mosaic of tiny, irregular bone islands." On the other hand, the bones of the face and skull base are much more nearly normal. A small and relatively long thorax is common. Calcification has taken place but the ribs are delicate and flexible. They are frequently the seat of numerous fractures. Deformities in the spine are rare but kyphoscoliosis has been described by Kienböck[16] and Niklas[23]. The pelvis may, to some extent, take the form so typical of osteomalacia.

"The stability of the skeleton is markedly diminished and instead of acting as a framework for the body, it is the most delicate and fragile part" (Nathan). Fragility is common to all the bones but fractures are almost entirely confined to the long bones of the extremities and to the ribs. The bones present an absolutely unique outward appearance. They are grossly deformed showing sharp angulations, irregular curves and, most striking of all, numerous annular thickenings due to callus formation following fractures. Hohlfeld[15] likens the long bones thus changed to a bamboo rod. Kienböck[16] divides the so-called fractures into fissures, infractions and true fractures. It is usually stated that callus formation is prompt and healing takes place in many cases more quickly than normal. The periosteum is but rarely ruptured. Kienböck, however, contends that healing is characteristically slow and may not be complete even after several months. He also states that instead of union actual resorption of the ends of the fragment often takes place. Sometimes in the place of a firm callus there exists an encircling band of decalcified bone. Similar and even more extensive changes result when dislocation of the fragments is present. The callus is largely of periosteal origin. In the late stages of the disease, according to this author, the periosteal callus may be greatly hypertrophied. The total number of fractures as indicated by the number of calluses present is extremely variable but frequently thirty or more. Mixsell[21] quotes the case of Chaussier with 113 fractures.

The microscopic changes in the bones have been carefully studied by Stilling[29], Harbitz[13], Michel[20], Biggs[3], Ziegler[32], Looser[18], Lovett and Nichols[19], Sumita[30], Fuchs[10], Frangenheim[9], Nicklas[23], Kienböck[16], Mixsell[21] and others. On section the bones are soft and porous but these changes are confined to the shaft. The epiphysis and epiphyseal cartilages are

normal in form and structure until in the later stages the cartilage may give evidences of degenerative changes. Most observers have found normal enchondrial bone formation but sometimes small in amount.

The cortex is commonly thin and friable. The spongiosa shows very unusual general markings. Here and there are seen small irregular islands of cartilage. Entire absence of trabeculae is often noted and if present they are small, irregular in outline and imperfectly laminated. Osteoblasts are much diminished in number and size and appear to deposit only a thin layer of osteoid tissues which is incompletely calcified (Nathan). Some authors have found the osteoclasts greatly increased. The periosteum is thin and functionally inactive. Large marrow spaces replace the normal Haversian system (Nichols). Biggs[3] has pointed out the important fact that the absorption of bony tissue is not replaced by organized connective tissue as in osteomalacia. Microscopically the relative amount of lime appears to be normal. Fibrous metaplasia is present in the marrow and the medullary canal is often dilated. Cysts are not seen.

This process in the bones is interpreted by Niklas[23] as "concentric atrophy caused by lack of bone apposition where the resorption is normal," by von Lobstein[17] as "inertia of function as regards bone growth," by Frangenheim[9] as "faulty bone formation," by Looser[18] as "faulty bone apposition or high grade atrophy and faulty thickness growth," by Fuchs[10] as "high grade periosteal dystrophy." The internal organs, central nervous system and endocrine glands are always without significant changes.

Symptoms

The general symptoms are few and seldom striking, in fact there are no characteristic constitutional symptoms. Until the disease is advanced, *i.e.*, until multiple fractures have occurred, even the deformities are not marked. With occasional exceptions the general health is good and the mentality normal.

The general appearance of the patient (Fig. 11) conforms to a moderately definite type. The head appears large in comparison with the body and the skull shows but little ossification. By contrast with the large skull the face is small but otherwise normal. The neck is short. The thorax is small though symmetrical and deformed only as a result of the rib fractures. A variable degree of protrusion of the abdomen is present. All of the extremities are small, delicate, short and show all degrees of deformity in accordance with the number of fractures. Throughout the body the skin is very delicate, somewhat pale and in many places thrown into folds. There is often a demonstrable increase in the subcutaneous tissues. The hair is abundant and silky. Profuse general sweating has

been noted (Segawa[28]). Such changes are less marked in the form which develops in early childhood. These infants appear normal at birth but at the end of the first or second year first show fractures and subsequently secondary deformities of the arms and legs. Widespread muscular atrophy including the heart was noted by von Lobstein[17]. Ankylosis may finally result but is exceedingly rare.

Eddowes[8] in 1900 first described an azure or deep blue tint to the sclera of many of these cases which he explains on the basis of a "deficiency of fibrous tissue in the sclerotic coat, whose thinness and transparency allow the underlying choroidal pigment to be seen." This sign (blue sclerotics) has been repeatedly recorded in published cases.

Fractures

Multiple factures of various kinds form the constant and most characteristic symptom. An extreme degree of brittleness in the bones as indicated by the number of fractures is present. The fractures are singularly bilateral. A single case of true osteogenesis imperfecta affecting the bones of only one side of the body has been reported by Adams[1]. Fractures are confined almost strictly to the long bones of the extremities and ribs, although the bones of the shoulder girdle may occasionally show the same lesions. The single bone most commonly affected is the femur. Among the various accidents to the bones an actual complete transverse fracture is the most frequent. In a few cases a new break has occurred at the point of an old one. The local reaction of pain, swelling, tenderness and muscular spasm common to fractures is absent or insignificant. Crepitus is less evident than in fractures of normal bones. Deformities result precisely as in normal fractures from healing with the fragments in bad position. The amount of callus formation is very variable in size but in most instances it is probably deficient. Where the callus is normal, union takes place promptly. Kienböck[16] emphasizes the slow and incomplete healing as particularly characteristic of the disease. The cause of the fracture is usually some form of slight, indirect violence. Some appear to be actually spontaneous. So exquisite is the fragility of the bones that even the most careful handling of the child may produce one or more fractures. Paralysis, incoordination, areas of analgesia, and anesthesia and nystagmus have been described (Biggs[3], Segawa[28], Hess[14]).

X-Ray Findings

The characteristics of the bones as shown in roentgenograms are distinctive and of the first importance in differential diagnosis. The main

features in a well developed stage of the disease may be summarized as follows (Lovett and Nichols[19], Mixsell[21], Biggs[3], Bamberg and Huldschinsky[2], Kienböck[16], Blaine[5], Niklas[23], Hess[14]): (1) a high degree of osteoporosis uniformly affecting the entire skeleton, the variations in density giving a mottled appearance; (2) marked deformities of the long bones of the extremities usually of an angular type and due to evident fractures, rarely also some actual bowing; (3) apparently normal size and shape of bones except as altered by fractures and resulting callus formation; (4) often excessive callus formation with variable degree of calcification. A transverse area of decalcification is often seen at the point of previous fracture; (5) the epiphyseal line is straight, cartilage often thin; (6) a very faint shadow is given by all bones, frequently scarcely more dense than the surrounding soft parts; (7) the cortex is thin, irregular and deficient in lime salts; (8) the spongiosa of both epiphysis and diaphysis is extremely faint with entire absence of all normal markings; (9) the medullary cavity is very irregular in outline and dilated.

Metabolism

Bamberg and Huldschinsky[2] studied the metabolism in an infant with osteogenesis imperfecta and found a definite nitrogen retention as well as a diminished daily excretion of phosphorus in the urine and feces. In the case of both nitrogen and phosphorus the excretion was markedly increased by the administration of phosphorus and cod liver oil. During the first ten day period of their experiment there was a negative balance in the lime which in later periods showed a positive balance. The excretion of lime was also favorably influenced by the phosphorus cod liver oil preparation. Schwarz and Bass[27] did similar experiments in a case of the congenital type and found the "nitrogen metabolism approximately normal and the fat retention and absorption normal." There was a positive calcium balance though somewhat below normal, *i.e.*, 109 mg. as against a normal of 120 to 210 mg. The metabolism of magnesium and phosphorus was within normal limits. Sodium and potassium both showed a positive balance but the significance of the retention is unknown. In Bookman's two cases the phosphorus retention was considerably increased above the normal while the magnesium retention was low. His conclusions respecting the calcium metabolism in osteogenesis imperfecta are: "(1) In active cases the calcium retention is somewhat below or very decidedly below the normal; (2) It is probable that variations in the course of the disease cause a change in the calcium balance; (3) The deficient retention of calcium is apparently influenced favorably by cod liver oil and phosphorus and still more strongly by calcium lactate."

Course and Prognosis

The prognosis varies somewhat with the different types of the disease and the intensity of the process but is on the whole bad. In the early form the mortality is nearly 100 per cent. (Bamberg and Huldschinsky), the majority dying in utero and the remainder soon after birth. Nathan[22] takes exception to this opinion and presents evidence to show that the disease is much less fatal than usually claimed. It is said that these infants are more susceptible to secondary infections, especially bronchopneumonia and frequently succumb to such complications. The later the symptoms appear the better the chances of recovery. The usual course in those who survive is a gradually increasing deformity of the legs with successive fractures during the first few years of life. Subsequently the child may learn to walk and enjoy good general health. The fractures tend to become less and less as the patient approaches adult life. Ostheimer[24] collected 193 cases from the literature and found that in 76.5 per cent. the last fracture occurred before the twenty-second year, yet fractures are recorded as late as thirty-three, thirty-eight and forty-one years.

Regarding the irregular course Kienböck[16] says, "The affection may undergo repeated florid stages and involutions during the whole period of its existence, thus showing irregular fluctuations; and there may be recurrences many years after apparent cures."

Diagnosis

Osteogenesis imperfecta of the congenital type and in its typical form with multiple fractures offers no resemblance to any other disease seen in this period of life. No other congenital disease shows general bone fragility. Neither is there any difficulty in differentiating the disease from other affections in infants and older children with which it is sometimes confused. The numerous fractures following slight trauma or occurring spontaneously and the characteristic X-ray appearances described above should leave no question of the nature of the condition.

The superficial resemblance of osteopsathyrosis to achondroplasia is sometimes confusing and the relationship between the two is probably a fairly close one. They are readily differentiated, however, as the similarity in appearance is confined entirely to the outward changes in the skin and subcutaneous tissue. But even these alterations are much less marked in osteopsathyrosis. The two conditions are the exact opposites from the

point of view of the nature of the disease process, *viz.*, achondroplasia results from a distorted function of the enchondrial ossification process while in osteogenesis imperfecta the normal function of the periosteum and osteoblastic cells fails (Sumita[30], Porak and Durante[25]). The very short legs, the result of retarded growth, which are so characteristic of achondroplasia are never seen in osteopsathyrosis except as they may be somewhat shortened in consequence of fractures and bowing. The tubular bones in achondroplasia are short, plump and sclerotic. Moderate bowing may be present but fractures do not occur. X-ray examination not only brings out these differences in the forms of the bones in the two diseases but in the finer structure as well. In achondroplasia, furthermore, the process is prominent in the base of the skull, vertebrae and pelvis. Ossification is complete in the skull and the sutures are normal or prematurely synostosed. Finally, the patient with increasing years remains a dwarf.

Fractures may very rarely occur in rickets and congenital syphilis but there seems no excuse for confusing either condition with osteogenesis imperfecta. Rickets is never congenital. Fractures when present are only one or two in number and the result of considerable violence. The fractures are not intraperiosteal as in osteogenesis imperfecta and the callus formation is very slight. Both clinically and anatomically the two processes are absolutely different. X-ray appearances are equally distinct. In neither the congenital nor the later form of syphilis in childhood is there any resemblance to osteogenesis. In the first form the lesion is primarily an osteochondritis while in the later the cortex of the long bones is the part attacked, the result being a thickening or hyperostosis of the cortex.

Treatment

Favorable results have followed the administration of phosphorus and cod liver oil and a rational basis for such therapeusis would seem to be found in the results of the metabolism experiments quoted above. The following combination may be used (Hess): Phosphorus 0.01 gm. and cod liver oil 60 c.c. or pure tribasic calcium phosphate 6 gm. and cod liver oil 60 c.c. The dose of each is 4 c.c. twice daily. The use of arsenic, iron, strontium, calcium, thyroid, suprarenal and pituitary preparations has proved useless. Czerny[7] has recently reported benefit from the use of raw carrot juice (100 grams daily). He bases his method on the theory that osteopsathyrosis is an avitaminosis and that the improvement in his cases was due to the vitamins of the carrot.

Prophylactic treatment designed to prevent fractures is important. As a special method of protection some have advised the use of braces in

the most severe cases. When fractures occur they should be treated like any fracture, great care being exercised that the fragments are in good position in order so far as possible to prevent the usual deformities. A careful hygienic-dietetic-regimen should be carried out in all cases. Massage is indicated for the muscular atrophy.

Part V

OSTEOMALACIA

Introduction

Definition.—An acquired disease of a chronic progressive type, usually seen in adult females, appearing in several forms and with varied clinical manifestations but characterized especially by general muscular weakness and pain referred to the bones. Pathologically the essential lesions are in the skeleton and consist primarily in a widespread softening and absorption of preexisting bone (halisteresis) and the formation of uncalcified new osteoid tissue. The process leads to marked deformities through bending and fractures.

The lesions in the bones which are seen in osteomalacia are found in many of the other diseases of the bones such as rickets, osteitis fibrosa, osteitis deformans, osteopsathyrosis and neoplasm, various diseases of the central nervous system (tabes dorsalis, syringomyelia, chronic myelitis and tumors), and by many authors the condition is considered a syndrome rather than a distinct and well defined disease. Bernard[2], for example, says, "one cannot consider osteomalacia a morbid entity, due to a sole and constant cause." It is rather "an anatomical clinical syndrome, corresponding to the osseous decalcification." He considers that osteomalacia and rickets represent the same syndrome with varying degrees of intensity and different localizations, but possessing the same "anatomic substratum," *i.e.*, decalcification combined with reaction on the part of the osteogenic elements of the bone marrow. In several of the above named diseases, rickets, osteitis fibrosa and osteitis deformans, the absorption of old bone and deposit of osteoid tissue poor in lime salts are prominent features and they undoubtedly bear a close relation to osteomalacia. Some writers have even considered them as varieties of a single disease.

Occurrence and Geographical Distribution.—In the United States the disease is among the most rare of the bone affections and the literature contains but few examples. It is much more common in Italy, Germany,

Switzerland, France and India. As in the case of goiter, osteomalacia is very frequently met with in certain limited districts, as the Ergolzthal in Switzerland and several of the districts in northern India. In England and other countries the disease is seldom seen and in Japan is practically unknown. A few observations indicate that in some countries it is most prevalent along river valleys. Osteomalacia is known to occur in the lower animals, especially in cattle and sheep.

Clinical Varieties

Many attempts have been made to divide the cases into separate groups but without complete success. The disease as observed at different ages and during pregnancy shows no essential clinical differences but in a general way it is possible to classify cases according to the period of life when it appears and with reference to pregnancy.

Puerperal Form.—By far the vast majority of cases occur in pregnant women or during the period of lactation.

Non-puerperal Form.—The clinical features and pathological changes seen in the non-pregnant women and in men do not differ from the above except that they are usually much less severe and the process is less predominant in the pelvis and more widespread. The non-puerperal form is also less apt to show remissions and exacerbations. Males seem to be as frequently attacked as females in this form.

Juvenile Osteomalacia.—Much confusion exists regarding the disease in children and some doubt its existence in the early years of life. Undoubtedly some of the reported cases were confused with rickets, but a sufficient number of examples of true osteomalacia have been reported by careful observers to establish the fact that the disease may occur at the time of adolescence (Fig. 13). Zesas[30] states that osteomalacia does occur during the first few years of life mainly following trauma, bronchopneumonia and the infections.

Senile Osteomalacia.—The considerable number of cases of osteomalacia in individuals past middle life reported during the past twenty years indicates that the senile form is not so rare as formerly believed. The onset is more gradual, although it is sometimes sudden, the course often prolonged and the symptoms less severe. Schiffmacher[25] says, "in the beginning of the senile period osteomalacias may appear, the symptoms of which are not all identical with those of puerperal osteomalacia and which must be carefully differentiated from the ordinary osteoporosis." Drasche[5] mentions the chief distinguishing clinical feature which separates it from osteoporosis as the flexibility. Like the juvenile form the alterations in the pelvis are not so prominent. Complications by conditions common to old age and especially

those associated with arteriosclerosis may obscure the picture of the osteomalacia.

Zesas[30] speaks of still another form due to diseases of the central nervous system (tabes, syringomyelia, chronic myelitis and tumors) which he calls "neurotic malacia" and which he explains as "trophoneurotic disturbances of the nutrition of the bones."

Etiology

There is no good evidence that heredity is of any importance etiologically.

Age.—Osteomalacia is primarily a disease of early adult life, in the majority of cases the first symptoms appearing between the twentieth and thirtieth years. Scott[27] found the average of cases in India to be 20.7 years. A few typical examples of the disease have been reported in individuals under twenty, chiefly at the time of adolescence and most authors now recognize a juvenile form. Its occurrence in infancy is still a matter of dispute. The incidence of osteomalacia after thirty is much greater than under twenty years. Zesas[30] quotes figures on this point. Among 247 cases, twenty-two, or nine per cent., were over forty-five years of age. Even extreme old age is not exempt.

Sex.—The overwhelming majority of cases occur in women. Only thirty-nine of a total of 360 cases collected by McCrudden[15] were in men. Scott gives the ratio of males to females in India as 1:50.

Pregnancy.—The close relation between osteomalacia and pregnancy and lactation is unmistakable but the precise part played etiologically by these conditions is a matter of much difference of opinion. Guthrie[9] quotes Sitzmann and Durham as having collected 132 cases of osteomalacia of which 91 were associated with pregnancy. The disease seldom develops in primiparae and seems to be more prevalent among women with very frequent pregnancies. The average number of pregnancies in the cases studied by Scott was 3.8, and the same author gives the figures for Italian cases as five. It is a common clinical observation that the disease first appears in a mild form and frequently seems to disappear after lactation is finished but reappears in a more severe form with each succeeding pregnancy.

A bewildering number of theories as to the cause of the disease have been advanced but the majority are based on mere clinical and often inaccurate observations. It is only within very recent years that the chemical studies of various authors, and especially the brilliant work of McCrudden, have thrown some light on the problem.

1. Such general factors as environment, general hygiene, social status, general habits of life and diet have often been mentioned as possible causes of osteomalacia. Statistics show that the disease is very definitely more

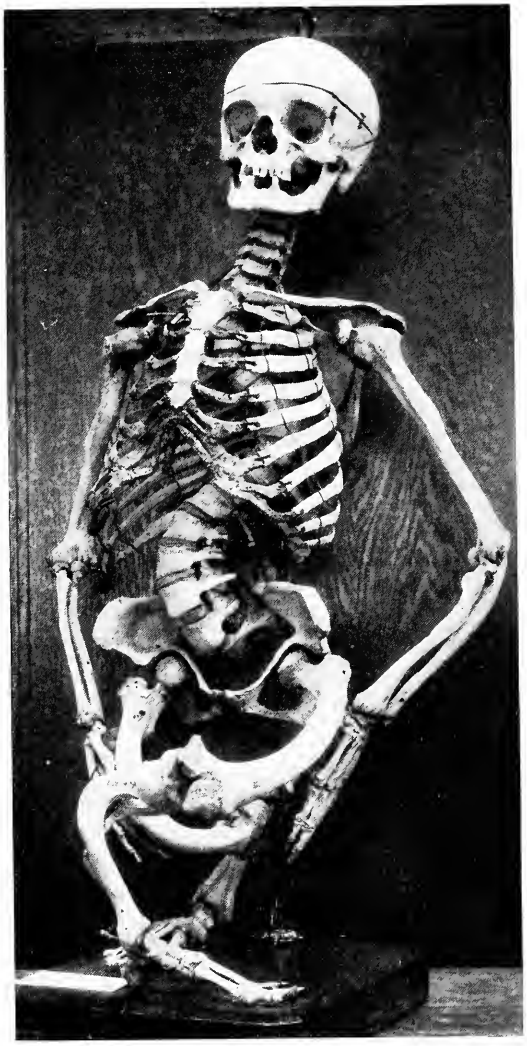

FIG. 13.—Osteomalacia. Skeleton of adult. (Warren Museum, Harvard Medical School.)

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common among the poorer classes and those who live under unhygienic surroundings but it is also found among the well-to-do. The prevalence of the disease in certain limited localities also suggests the possible influence of some of the above factors. Similar evidence exists in the case of cattle. Osteomalacia, for example, is endemic in the region of Augsburg where the soil is found to contain fifty to sixty per cent. of pure carbonate of lime but is poor in phosphoric acid and the fodder is markedly deficient in calcium phosphate (Zesas). Numerous feeding experiments in animals of various species have shown that osteomalacia can be produced by prolonged feeding with a calcium-free diet. A very careful study of diet as a possible etiological factor in cases occurring in India was made by Scott[27] and with negative results. The application of these observations is, however, a very limited one and any role which they may play in causing osteomalacia through faulty nutrition must be a very minor one.

2. One of the oldest hypotheses is that the process of absorption in the bones is the result of the action of some acid contained in the blood or tissues which dissolves out the mineral constituents. Lactic, oxalic, acetic, formic and carbonic acids have in turn been suggested. For many obvious reasons this theory is absurd and mention is made of it only because of the prominence which has been given it in the literature of osteomalacia.

3. The course of the disease, the nature of the changes in the bones and the fact that it is known to follow such infections as scarlet fever, pneumonia, rheumatic fever, influenza, syphilis and typhoid have suggested that the disease itself may be caused by some specific organism with or without antecedent trauma. Many authors regard the disease as probably an infection and the softening in the bones, the result of the presence of microorganisms or their toxins. Petrone[20] in 1892 claimed to have isolated an organism ("micrococcus nitrificans") which when injected into dogs caused bone changes characteristic of osteomalacia. Arcangeli[1], in 1902 and 1907, made similar claims for a microorganism which he named "diplococcus osteomalacia hominis." He reports a cure in thirteen cases by the use of vaccines prepared from this diplococcus. The work of these authors has not been verified and the theory finds no support either in the clinical facts or the post-mortem studies.

4. Much evidence points to the cause of the disease in some disturbance of function in the glands of internal secretion (ovary, suprarenals, thyroid, parathyroid and hypophysis) which directly or indirectly affects the metabolism in the bones. Hoennicke[12] considers that the disease is the result of disturbed function of the thyroid. He has observed one case and quotes several others showing an association of exophthalmic goiter and osteomalacia in the same individual. In certain localities where Graves' disease is prevalent, osteomalacia is also common. In other instances

thyroid symptoms may appear in the course of osteomalacia. Atrophy of the thyroid is known to lead to limitations in length and growth of bones, a consideration to which Hoennicke attaches much importance. This author states that the thyroid gland shows an abnormal structure in most cases of osteomalacia but pathological reports do not bear out this statement. He finds evidence for the probable association of the thyroid and ovary in producing the bone lesions, *i.e.*, the diseased thyroid inducing an increase in the excretion of phosphorus which is aggravated by hyperactivity of the ovaries and especially during pregnancy. The evidence which Hoennicke offers as proof of his theory is by no means sufficient and the theory has received but little support.

The publication of favorable results in osteomalacia from the administration of adrenalin by Bossi[3] in 1907 seemed to offer excellent evidence of a probable cause of the disease in a deficiency in the suprarenal glands. This probability might seem further emphasized by the known influence of the secretion of the suprarenals on the ovarian activity and the general belief that the adrenal secretion influences bone metabolism. It seems fair to say that the theory of the dependence of the marked disturbance in the bone metabolism in osteomalacia on alterations in these glands rests on no firmer basis than the evidence of empirical treatment.

Of all the endocrine glands the ovary would seem to stand out as the one most probably concerned in the morbid process in osteomalacia. The occurrence of the disease in the great majority of cases in women during pregnancy, the "physiological osteomalacia" of Hanau[10], which is known to occur in many normal women during the later months of pregnancy and the supposed striking improvement following removal of the ovaries in osteomalacia all point strongly to this organ as concerned in the etiology. Fochier[8] in 1879 when performing a Caesarean section on a case of osteomalacia removed the uterus and ovaries. The case recovered from the osteomalacia and on the basis of this experience Fochier recommended the oöphorectomy for the cure of osteomalacia, his theory being that the disease is due to a hyperactivity of the ovaries. Fehling[7] in 1894 reported the first series of cases treated by this method and claimed extraordinarily favorable results. McCrudden[47, 46] has made a very exhaustive and scientific investigation of the relation of the ovaries to osteomalacia. His numerous experiments on animals establish the important fact that castration has no effect on the general metabolism. A case on whom castration was done was studied before the operation, a few months later, and a year subsequently. The removal had no beneficial effects on the osteomalacia and the metabolism was unchanged. McCrudden[15] further made a critical study of the cases reported in the literature treated by oöphorectomy and found but a small percentage with evidence of cure. He very reasonably raises the

question, "if osteomalacia is due to overactivity of the ovaries, it is difficult to understand how a patient without ovaries can have osteomalacia." The importance of castration in these cases is, as McCrudden suggests, that it prevents further conceptions which are so apt to be accompanied by severe exacerbations of the disease. This appears to be sufficient proof, as McCrudden contends, that "osteomalacia is not a disease of the ovaries."

McCrudden[15,18] has worked out a complete explanation of the bone changes in osteomalacia which in every respect is consistent with the known facts regarding the disease and which, it seems probable, will find general acceptance. This author finds abundant proof in the chemical and pathological studies made of Cohnheim's conception of bone as a living tissue which undergoes anabolism and catabolism like any other living tissue. When this interpretation is applied to the process in osteomalacia we see not a simple halisteresis of bone as claimed by Virchow and others but absorption of old bone plus an active anabolism in the formation of new osteoid tissue poor in lime salts. The laying down of new osteoid tissue is entirely in accord with the repeated demonstration of the retention of sulphur and magnesium in relatively greater amounts than the nitrogen as the tissue formed is unusually rich in these two elements. As this new bone is very poor in lime and as the old bone is being rapidly decalcified and absorbed there is an increased excretion of calcium. In osteomalacia there is evidently a more or less severe disturbance of the normal balance of the anabolic and catabolic processes in the bones. How this disturbance comes about is the key to the etiology. The osseous system may be regarded as a storehouse of lime. During pregnancy there is a greatly increased need for calcium to meet the demands of the developing bones of the fetus and this call is met by the increased catabolism of the maternal bones. It is important at this point to recall the results obtained by Hanau[10], namely, that the bones of apparently healthy pregnant women are often deficient in lime salts, *i.e.*, changes similar to those found in osteomalacia but less severe have taken place, a "physiological osteomalacia" so-called. The chemical analysis of the bones and the study of the metabolism in osteomalacia give results in support of this. The bones are relatively poor in mineral constituents, especially phosphate of lime, and relatively rich in organic matter. Metabolism studies show an increased excretion of calcium and a retention of sulphur and magnesium. During the early stages of puerperal osteomalacia there is an actual retention of calcium. McCrudden has shown that to a certain degree the calcium phosphate is replaced by magnesium phosphate.

A further observation forms another important link. Osteomalacia rarely begins until after the second or third pregnancy and then as a rule in women of poor general nutrition and whose environment is unhygienic. The patient often recovers from the first attacks but suffers a remission with the

next pregnancy, the condition becoming exaggerated with each succeeding one. "In other words, it is only after a long continued and severe drain on the bones of a poorly nourished patient that the body fails to respond to the demands on it and even then recovery follows if the severe demands are not continued. . . . After repeated, rapidly following pregnancies, the amount of calcium phosphate in the bones becomes less and less. A new pregnancy begins before the organism has made up for the loss of calcium phosphate in the preceding pregnancy. . . . The condition of greatest importance would seem to be a marked tendency to overprolongation of the period of calcium flux" (McCrudden).

The cause of the disease in the non-puerperal form is somewhat less clear. McCrudden[15, 18] cites the calcification of various tissues (dura, pia, choroid, muscles, bladder, lungs, pleura, stomach, liver and lymph nodes) and the heteroplastic bone formation occasionally observed and argues that some such prolonged demand for calcium increases the catabolism in the skeleton and upsets the metabolism balance. He suggests the possibility that the process once started may continue after the primary need has ceased.

Pathology

The affected bones in osteomalacia are abnormally soft, pliable, friable, easily cut with a knife, and consequently deformities and fractures are common. As the process in the individual bones proceeds unequally the deformities may comprise the entire bone or only a portion. In the long bones particularly, bowing of an irregular, angular type is very characteristic but in sharp contrast to the even broad curves seen in osteitis deformans (Fig.. 13). As a result of the extensive decalcification and absorption the diseased bone is much lighter than normal bone.

In the puerperal form the pelvis is the part of the skeleton most frequently attacked but in the majority of cases the spine is also involved. The bones of the thorax stand next in order followed by the long bones of the extremities. Involvement of the skull is rare. In the non-puerperal form the pelvis, spine, ribs and the long bones of the extremities are affected with about the same degree of frequency. The skull not infrequently participates. The characteristics of the deformities in the individual bones are important as they are for the most part unlike those seen in any other disease. The pelvis shows the greatest change in form. The sacrum under the weight of the body is forced downward while the pelvis is compressed laterally forcing the symphysis forward to form a sharp angle. The outlet of the pelvis is in consequence greatly contracted and to greater extent than the inlet, yet in spite of this the bones are so pliable that normal delivery may take place.

The form of the pelvis is often spoken of as heart shaped or cloverleaf in form. To a considerable degree the ultimate form of the pelvis depends on the position assumed for a long period while the patient is confined in bed. Marked and extensive changes in the spine are particularly common. The individual vertebrae are compressed, misshapen and displaced; hence a considerable shortening of the vertebral column. There is a combination of lateral curvature with an accentuation of the normal curves which is sometimes extreme. The changes in the thorax do not conform to any definite type. Through bending of the spine, clavicles and sternum, as well as numerous fractures and deformity of the ribs, the whole thorax may be greatly distorted and cause displacement of the intrathoracic organs. Severe subjective symptoms often result. Involvement of the extremities though less severe and later in developing than the above is nevertheless usually present in all severe cases. The arms seldom show as marked alterations as do the legs. The femur and tibia are most commonly involved. Irregular and asymmetrical bending with fractures is seen but rarely any considerable enlargement since callus formation is practically wanting. The skull is sometimes attacked but is never deformed.

The outer surface of the bones is uneven and in many places injected. On section the entire structure seems to be altered, almost nothing remaining of the normal bone architecture. The cut surface is yellow or red in color and is generally hyperemic or with ecchymotic areas. The normal trabecular structure is nearly wanting while the marrow spaces are enormously enlarged and filled with altered marrow. Small cysts filled with yellowish or bloody fluid are occasionally seen. The cortex, especially in the long bones, may be a mere thin shell or entirely absent. The periosteum is adherent, somewhat thickened and hyperemic.

On microscopic examination the trabeculae are seen to be thin and widely separated. The central portion of the trabeculae in many places retains the appearance of the normal bone but is surrounded by the decalcified material. The perforating canals are numerous, dilated and surrounded by the same calcium free tissue. Schmidt[26] interprets the appearances as indicating that the lamellae where crossed by the perforating canals have become decalcified thus leaving an encircling zone of osteoid tissue. This process begins in the medullary portion of the bone. The new osteoid tissue, which is often extensive, is formed largely from the proliferating medullary membrane but to some extent also from the periosteum (Schmidt[26], Tashiro[29]). Osteoclasts are present in moderate numbers in the osteoid tissue (von Recklinghausen[22], von Ribbert[24]). The bone lesions were formerly interpreted by Virchow, von Recklinghausen and others as solely the result of halisteresis but later studies have proved that much of the abundant osteoid tissue is not due to this process but to the laying down of uncalcified new bone. Von Reckling-

hausen[23] has in a later publication accepted this view of the double origin of the osteoid tissue. The marrow appears much more hyperemic than normal and is particularly rich in cells. Hemorrhage into the bone marrow can be seen in many places. No constant changes occur in the epiphyseal cartilage.

The joints remain unchanged at first but finally undergo moderate atrophy resulting from disuse. In the final stage extensive ankylosis often forms, the muscles show general atrophy and fatty degeneration. Various abnormalities have been found in the ovaries and thyroid but none which are constant and characteristic.

Chemical Composition of the Bones in Osteomalacia

In recent years McCrudden[13,17,18] has made very exhaustive chemical studies of the bones and reviewed the entire subject. Briefly summarized, the results of these bone analyses show a constant decrease in the proportion of inorganic constituents and a corresponding increase in the proportion of organic constituents. McCrudden finds the increase in the percentage of organic constituents much greater than can be accounted for on the basis of decalcification alone and interprets this fact as direct and important evidence in support of Cohnheim's conception of bone as a living tissue. The relatively large proportion of organic constituents can be accounted for, in other words, only on the theory that new osteoid tissue is formed coincidently with the decalcification of old bone.

The figures for numerous analyses given by McCrudden show moderate variations but the average gives a loss of calcium in the dried bone to approximately one-half the normal. Phosphate is decreased also but to only about two-thirds the normal, making the P_2O_5:CaO ratio in osteomalacia somewhat higher than normal. The magnesium and sulphur were more than four times the normal and he explains this as the result of increased deposition of new bone, the magnesium to supply the deficiency in calcium and the sulphur as a normal constituent of the organic matrix.

Symptoms

The disease is scarcely ever recognized until it has reached a well developed or even a late stage. This is perhaps partly due to the fact that osteomalacia is a rare malady and its symptoms are not familiar to physicians generally. A more important reason is that the onset is gradual and irregular. Until the process in the bones has reached the point where deformities and fractures occur or until sufficient changes have taken place to give typical appearances in the X-rays a diagnosis is hardly possible.

The earliest and most constant symptom is pain which varies from a dull rheumatic type to intense neuralgic. The common seat of the pain is the pelvis, back, hips, thorax, neck, extremities or the hip and knee joints. These pains are more acute at night, at the time of the catamenia and are aggravated by movement or pressure over the bones. When the spine is involved the patient often suffers from girdle pains. In pregnant women particularly the first indication of the disease is apt to be constant dull pain in the pelvis which is increased by walking or sitting for a long period in one position. Cramps and spasms of the muscles may follow or in occasional cases are the initial symptoms. The muscles of the leg, especially the adductors and flexors of the hip and knee, are held rigidly to prevent movement. As a result it is hard to straighten the legs in bed and walking and climbing stairs become difficult. The gait is a peculiar, characteristic shuffle and is sometimes spoken of as the duck gait. The advancing leg is jerked or dragged forward without raising the foot from the floor, which gives a curious spastic or waddling appearance. Muscle fatigue is easily induced. Exaggeration of the reflexes, disturbances of sensation, intention tremor and even paralysis may accompany the above symptoms. Scott[27] quotes a case in whom the onset took the form of a tetanoid attack followed by cramps and stiffness in the legs.

The objective symptoms in a well developed case of osteomalacia are extremely variable depending on the part of the skeleton most involved. Deformities (Figs. 13 and 14) are striking and appear relatively early in the course of the disease. In consequence of the lordosis, kyphosis and scoliosis of the spine together with the compression of the pelvis there is a very evident diminution in height. The thorax is distorted, the commonest changes being a lateral compression with resulting increase in the anteroposterior diameter and protrusion of the sternum (pigeon breast). The clavicles are strongly arched. Frequently many of the ribs become fractured causing a local depression of the chest. Just below the lower limits of the thorax in the lumbar region is a deep transverse groove due to the shortening of the spine. The pelvis is most commonly involved of all the bones and presents a fairly constant type of deformity. It has been described as crumpled. There is both a downward and lateral compression, the sacrum being forced downward and forward and the iliac bones pressed inward. The ischial tuberosities are brought nearer together. The symphysis pubis protrudes anteriorly, the duck bill form, so-called. The long bones of the legs are more affected than those of the arms (Fig. 13). The femur and tibia especially are irregularly curved, the bowing being usually forward. Genu valgum is often present though genu extrorsum does occasionally occur. Multiple fractures may lead to very great deformities especially since only a very small callus is usually formed.

Menstruation is usually normal and osteomalacic women are considered to be abnormally fertile. In the early stages parturition is normal but with each succeeding pregnancy delivery becomes increasingly difficult and finally is possible only by Caesarian section.

In the late stage of the disease the patient becomes bedridden and the deformities reach a more and more extreme degree as the result of fractures and muscle contractures. At this stage ankylosis and distortion of the joints take place. Muscle wasting becomes extreme and finally severe cachexia supervenes. Functional disturbances follow, bronchitis, dyspnea, palpitation, edema, digestive disturbances, fever, hyperhidrosis, psychic instability and disturbances of secretion. The patient looks prematurely old. Decubitus may develop.

The blood undergoes no significant changes. Varying degrees of anemia may develop in the severe cases. Eichorst[6] mentions an increase in the myelocytes and eosinophils in occasional cases. Hyperleukocytosis has been present in a few. Scott[28] examined thirty-seven cases with reference to the amount of calcium in the blood and concludes that the calcium content of the blood is increased in osteomalacia but the rise is not influenced by pregnancy or lactation.

Many reports have been made of lactic acid in the urine but McCrudden[15] condemns the chemical methods used. He has never been able to demonstrate this substance in the urine and states that there is no good evidence that lactic acid occurs in the urine in osteomalacia. Bence-Jones albumose is said to have been found in osteomalacia but it is probable that multiple myeloma was mistaken for this disease. Dock[4], however, mentions a personal observation of a typical case of osteomalacia in which the urine contained the Bence-Jones body. Scott[28] found an increase of 0.26 grams of calcium chloride per liter of urine (1.1 grams calcium chloride per liter being normal) in non-puerperal osteomalacia, and a deficit (0.988 grams) in the presence of either pregnancy or lactation. This deficit is interpreted by this author as indicating that the calcium is being withdrawn from the maternal bones to meet the demands of the growing skeleton of the fetus. No diagnostic or prognostic value can be given to the calcium and phosphates excreted in the urine as the amount is so variable. The content of these substances in the urine is often greatly increased but does not parallel the clinical course.

Metabolism in Osteomalacia

McCrudden[15] summarizes the results of his own and others' experiments as follows: "We find that the body is losing calcium and retaining magnesium and sulphur. These results are in accord with those obtained by bone

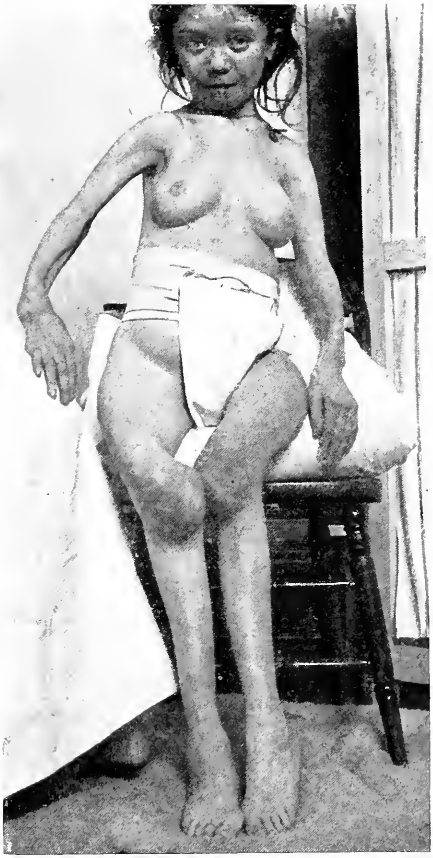

FIG. 14.—Osteomalacia. Girl, age 15. (Case of Dr. C. F. Painter.)

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analyses and confirm the supposition that in osteomalacia the process is not one of simple passive halisteresis, but an active one of increased bone metabolism. Old bone is destroyed and new bone laid down, but the new bone is similar to the organic matrix of normal bone and is free from, or poor in, calcium phosphate, instead of which there is a partial replacement of the calcium phosphate by magnesium phosphate."

X-ray

The X-ray appearances in the bones are peculiarly distinctive in well marked osteomalacia. They show extreme irregularity in the contour of the bones with broad or angular curves in the diaphyses. Fractures are often evident, usually with only a poorly formed callus or rarely none. The most striking characteristic is the extraordinary rarefaction of the bony tissue. It appears hazy, indistinct and offers almost no contrast to the soft parts. Only here and there is any trabecular structure evident. The medullary cavity is dilated and the cortex very thin. The epiphyses are generally transparent but free from deformities.

Course and Prognosis

The course of osteomalacia is variable. Most cases run a chronic course extending over many years. Occasionally periods of remission lasting for months or even a few years interrupt the progress of the disease but they are succeeded by exacerbations. In Scott's[27] series the maximum duration was thirty years and the average 6.5 years. The course is often determined largely by the number of pregnancies and the duration of lactation. Very rarely after the disease has progressed for some time a spontaneous cure results so far as further progress of the disease is concerned. Scott observed two such cases. Also in rare instances the disease runs a very acute course of only a few months. Ogata[19] gives a general death rate of 80 per cent. Hellier[11] calculated a mortality of 70 per cent. in the puerperal and 84.7 per cent. in the non-puerperal form. Death may result from cachexia or from cardiac failure or some intercurrent infection.

Diagnosis

Osteomalacia in its late stages presents such unique deformities that no possibility should arise of confusion with any other disease. Early in its

course, however, diagnosis is very often exceedingly difficult. The special diagnostic features are the age period, sex, the usual occurrence with pregnancy, the onset with severe pain and tenderness over the bones and early and peculiar deformities.

The diagnosis from osteitis deformans and ostitis fibrosa cystica has already been considered under those diseases. Late rickets as seen in adults does not give the severe pain and tenderness so constantly present in osteomalacia nor the type of deformities. The constant changes in the epiphyses and in the skull in rickets are never present in osteomalacia. Skiagraphs in the two conditions are entirely unlike.

Multiple myeloma may resemble osteomalacia in the stage previous to the development of marked deformities. Pain and tenderness over the bones are cardinal symptoms in both diseases. Bence-Jones albumose if present in the urine is pathognomonic of multiple myeloma. The pelvis and the spine are usually the first bones involved in osteomalacia while in multiple myeloma the first symptoms are apt to appear in the ribs.

Treatment

The closest attention to every detail of the general hygiene is of the first importance. A full nutritious diet rich in calcium and phosphorus (milk, eggs, meat, fish and especially green vegetables), rest, fresh air, hydrotherapy and massage will often bring about marked improvement. Gestation should be avoided and nursing forbidden. Particular care is necessary that the bed is of suitable type to give comfort to the patient and to lessen the progress of the deformities as well as the dangers of fractures. Mechanical supports of various kinds are usually indicated. Surgical measures are useless except in the treatment of fractures.

For several decades the chief interest in the treatment of osteomalacia has centered in measures concerned with the function of the ovaries and pregnancy. As early as 1876 Porro[21] reported a case of osteomalacia with apparent cure following the removal of the uterus and ovaries. Fochier[8] in 1879 strongly advocated this method. Fehling[7] in 1891 published the results in a considerable series of cases treated by castration done at the time of Caesarian section and recommended the procedure in severe cases. Since Fehling's report ovariotomy has been done extensively and the results have been generally favorable. Unquestionably many cases have been cured by castration. The favorable results were believed to be due to a retention of mineral substances in the body following castration. McCrudden has proved experimentally that castration is without effect on the general metabolism and his exhaustive work on the subject seems to show that the

improvement in osteomalacia after oöphorectomy is due entirely to the prevention of further gestation. The same end has been sought by the use of the X-ray to produce sterility and apparently with success. Sterilization would seem fully justified in the severe puerperal forms of the disease where repeated pregnancies have occurred.

Bossi[3] in 1907 published excellent results from the use of very large doses of adrenalin given subcutaneously (1 c.c. of a 1:1,000 solution every second day). The experience of many clinicians with this method has been variable. It is warmly recommended by some and condemned by others. This treatment is without a scientific basis and probably without merit.

The administration of phosphorus while purely empirical has been useful in the hands of many and seems to have a place in the treatment of the disease. It is usually given in 0.01 per cent. solution in cod liver oil, one teaspoonful three to six times daily and for a period of months. If well borne the percentage should be gradually increased to 0.05 or 0.06. Some prefer to use the phosphorus in pill form (Pilulae Phosphori, U.S.P. containing phosphorus 0.06 gm.).

Part VI

ACHONDROPLASIA (CHONDRODYSTROPHIA FOETALIS)

Introduction

Definition.—Achondroplasia is a relatively rare disease of the skeleton affecting only those bones formed from cartilage and invariably beginning in early fetal life. The characteristic features of the disease at birth are a moderately enlarged head, depression of the root of the nose, trident hands and remarkably short and curved extremities (micromelia), due to arrested development of the long bones, which contrast sharply with the normally developed trunk. In the few cases who survive, these characteristics become more accentuated and produce a type of dwarfism.

Synonyms.—Rachitis micromelica (Winckler, 1871); achondroplasie (Parrot, 1876); micromelia chondromalacia (Kirchberg and Marchand, 1889); chondritis foetalis (Eberth, Hoess, Urtel); pseudochondritis (Schidlowski); dysplasie crétinoide (Klebs); osteosclerosis congenita (Kundrat, Paltauf); periostale Aplasie mit Osteopsathyrosis (S. Müller); chondrodystrophia foetalis (hyperplastica, hypoplastica, malacica) (Kaufmann); mikromelia (Kassowitz).

In earlier writings the disease was often classified under the term osteogenesis imperfecta. In France the name achondroplasia has come to be

used almost universally while in Germany the term chondrodystrophia foetalis is more commonly employed. The latter implying a nutritional disorder of the cartilage in fetal life is more accurate than the former which signifies an entire absence of the normal activity of the cartilage in producing osseous tissue, which is not strictly the case in this disease. Achondroplasia has the advantage, however, of priority and common use.

Historical.—Unmistakable examples of this disease are recorded in medical writings for considerably more than a century, but until comparatively recent years it was wrongly classified under a variety of names but chiefly as fetal rickets or cretinism. The first case was described by Sömmering[28] in 1791, his report of the autopsy findings in the case of a deformed fetus making it clear that he was dealing with a typical example of this disease.

Romberg[26] (1817), Weber[34] (1829) and Busch[3] (1836) each recorded a case showing the salient features of achondroplasia. In each instance the author regarded the condition as fetal rickets. In 1856 Virchow[33] reported the first pathoiogical studies of such a case, also classifying the condition as fetal rickets. A few years later H. Müller[17] (1860) made an exhaustive study of several cases of the disease in both man and animals and showed that the disease was distinct from the ordinary form of rickets as seen in children. He differentiated a congenital form of rickets as exemplified by these cases. Certain cretinoid features were recognized in the cases studied and he admits a possible relationship between the two. Müller was the first to recognize the synostosis of the early bone centers at the base of the skull and to attribute the bone changes to a disease of the primordial cartilage. This important work marks the real beginning of our present knowledge of the disease. The same conclusions were reached by Winckler[36] (1871) and Urtel[31] (1873) from histological studies of a similar fetus, the former author suggesting the term "rachitis mit micromelia." Parrot[20] (1878) separated the condition entirely from rickets, congenital syphilis and cretinism and suggested the term achondroplasia. He defined the main process as a dystrophy of the primordial cartilage accompanying the first osteogenetic growth in the fetus.

The most important single contribution to the pathology of the disease was made by Kaufmann[13] in 1892–93. He advocated the name chondrodystrophia foetalis. This author on a pathological basis and as a result of most careful study of fourteen cases describes three forms as follows: (1) Chondrodystrophia hypoplastica in which the cartilage proliferation is diminished and the outward appearance of the epiphysis does not seem changed; (2) chondrodystrophia malacica, or chondromalacia foetalis characterized by a softening and breaking down of the epiphyseal cartilage; (3) chondrodystrophia hyperplastica due to an undisciplined growth of

the epiphyseal cartilage which is vascular and soft. The growth of the epiphysis produces a marked enlargement in the region of the joints. The bones are harder than in the other two forms and more prone to fractures.

A remarkably complete and accurate description of the clinical features of achondroplasia was published by Marie[16] in 1900. Many important contributions have been made to the subject in recent years and a summary of all these works is to be found in the exhaustive discussion of the disease by Rankin and Mackay[24] and Emerson[7].

It is impossible to make any exact statement regarding the incidence of achondroplasia. Notwithstanding the fact that it is the most common of the congenital bone affections it must be considered as relatively rare.

Etiology

Heredity is fully established as an etiologic factor of considerable importance. Marie[16], Emerson[7] and several other recent authors have presented abundant evidence from the literature of direct inheritance in achondroplasia. The most striking and frequently quoted case of Porter's[23] presents a record of six typical examples of achondroplasic dwarfs in three generations. All were males. Several authors have also recorded more than one achondroplast in a single generation. Emerson mentions a possible relationship between the disease and frequent and numerous pregnancies as seems to be suggested in the records of several cases. No recently compiled statistics regarding sex are available but a slight preponderance of females seems to exist.

Many possible causes of achondroplasia have been suggested, among them syphilis, tuberculosis, infection and chronic intoxications of an hereditary type, degeneracy, nutritive disturbances in the placenta, various mechanical factors in utero affecting the embryo and disease of the glands of internal secretion. Among earlier writers especially the disease was frequently regarded as a form of rickets or cretinism. Proof is entirely wanting in all these possibilities.

Jansen[11], in 1912, published an elaborate monograph in which he develops a theory of the nature and cause of the disease which seems worthy of very careful consideration. This author divides the special features of achondroplasia into two groups: (1) dwarf phenomena including the short extremities due to insufficient bone growth, persistence of the fetal type of hands, *i.e.*, divergence of the hand rays and resulting splitting of the fingers into groups ("main en trident"), deficient development of the pelvis, vertebral column, chest and, to a slight degree, of the bones of the basis cranii. These are the most evident characteristics of achondroplasia; (2)

phenomena of infolding or mechanical malformations. These symptoms though less conspicuous than those of dwarf growth are equally pathognomonic. They are purely the result of mechanical forces which modify the form of the fetus and include depression at the root of nose, shortening of the length and increase in the transverse diameter of the base of the skull, narrowing of the choana, dorsolumbar kyphos.

Jansen offers convincing evidence that the chief, if not the only factor in causing the infolding of the embryo lies in the amnion which is abnormally small. He explains that such power on the part of the amnion to infold the fetus is possible by the end of the third week. As direct amnion pressure causes infolding of the fetus, so indirect or hydrostatic amnion pressure produces the phenomena of dwarfism. In consequence of pressure growth is arrested as a result largely of cell necrosis. "Cartilage in achondroplasia which suffers from famine at its birth never outgrows the injury." The principle underlying the above as stated by Jansen is,"amnion pressure is able to disturb the nutrition and the growth of part of the embryo, whilst the non-affected parts continue their growth." Jansen further offers reasonable evidence that the so-called "non-characteristic" symptoms of achondroplasia (micrognathy, agnathy, harelip, athyreoplasia, hydrocephalus, gas bubbles in the lungs, kidney, thymus, liver and other internal organs, subcutaneous fatty masses and enhanced sexual activity) are also due to direct or indirect amnion pressure.

Finally Jansen formulates his thesis as follows: "the achondroplastic is an amnion dwarf, folded up by a dwarf amnion, by the enhanced hydrostatic pressure of which it has been disturbed in the development of its skeleton." Although further proof of the accuracy of this conception of the cause of achondroplasia is necessary, Jansen's brilliant arrangement of scientific data carries conviction and it seems probable that his explanation of the changes characteristic of the disease will ultimately be substantiated. Certainly this hypothesis is the only one among the many advanced which has a real scientific basis.

Whatever the uncertainties regarding the cause of the disease may be, the nature of the process is clear. As first pointed out by H. Müller and substantiated by many subsequent investigators the seat of the disease is in the primordial bone cartilage. The disease is primarily an "arrest or perversion of the normal processes of endochondrial ossification." The rows of proliferating cartilage cells are either wanting or their normal arrangement is much disturbed. The result of this distrophy of the bone cartilage is a marked diminution of bone production and consequently an inhibition of growth in the long bones. Those bones which develop from membrane (flat bones and vault of skull) or from cartilage late in fetal life are not affected.

Pathology

In consequence of the fact that achondroplasia usually runs a fatal course, *i.e.*, the individual dying in utero or soon after birth, abundant opportunity for pathological studies has existed and the literature is especially rich in pathological reports (Virchow[33], H. Müller[17], Parrot[20], Ebert[6], Apert[1], Kassowitz[12], Kaufmann[13], Porak[21], Porak and Durante[22], Schidlowsky[27], Durante[5], Grawitz[10], Kirchberg and Marchand[14], Regnault[25], P. Marie[16], Symington[29], MacCallum[15], Parhon, Shunda and Zalplachta[19], Opie and Allison[18], Symmers and Wallace[30]). No autopsy on an adult achondroplast has ever been recorded. The essential lesions of the disease are in the bony structures although certain and variable changes may be present in the soft parts.

General Deformities

The general appearances of the fetus with this affection are striking and entirely distinct from those seen in any other disease. A diagnosis can readily be made on inspection. The infant is usually plump and the thickened skin is thrown into folds especially about the joints, an appearance which Weber[34] describes as "a dwarf with much too large clothes." A disproportionately large head and normally developed trunk contrast sharply with the very short but usually well formed extremities. As a result of the micromelia or phacomelia the stature is much abbreviated. The depression of the root of the nose gives it a peculiar saddle form or pug nose appearance. The prominent lower jaw (prognathus), thick lips and protruding tongue suggest cretinism. A marked prominence of the abdomen is the rule. Throughout the body the changes are almost strictly symmetrical.

Individual Deformities

In the normal infant the central point of the body is at the navel but in the achondroplast the disproportion between the legs and trunk raises the point to the zyphoid cartilage. Instead of the average normal length of the fetus of 50 cm. (Kaufmann) these cases measure from 30 to 40 cm. and a few are recorded considerably under 30 cm.

The head shows a varying degree of enlargement and may be hydrocephalic (Fig. 15). Kassowitz[12] studied the relation of the circumference of the head to the body length and gives the figures for the normal new-born as 33 cm. for the former and 50 cm. for the latter; or a percentage of 66.6. He quotes figures for achondroplasia varying from seventy-five to one hundred

and twenty per cent.; in other words, in this disease the circumference of the head often equals or considerably exceeds the total body length. It should be noted, however, that the macrocephaly is often more apparent than real. The skull is not strikingly changed in shape except for a considerable prominence of the frontal region and a tendency to the brachycephalic type. In contrast to the condition found in osteopsathyrosis the cranial bones are well formed and hard and the fontanelle and sutures normal or permaturely closed.

The bones of the skull base are largely formed from cartilage; hence like the long bones they play a prominent part in the achondroplastic process. The changes are exceedingly variable, some parts being normal while others are abnormal. Premature union of the bones and arrest of development are the two most important conditions found.

The os tribasilaris (Virchow) at the time of birth is composed of three separate parts, the basilar portion of the occipital bone and the two portions of the sphenoid which are united by synchondrosis. The synchondrosis between the two sphenoids normally ossifies soon after birth but the synchondrosis between the occipital and the sphenoid bones does not become bony until adult life. These bones are often firmly united at birth in the achondroplastic fetus and according to most authorities it is this premature synostosis which is largely responsible for the retardation in the growth of the basis cranii and the resulting deformities. Likewise the bony union of the four bones surrounding the foramen magnum should not occur until about the sixth year but they are usually completely synostosed at birth in this disease. Jansen[11] is convinced that the usual conception that this synostosis is the cause of the shortening of the basis cranii is entirely erroneous and supports his opinion by convincing arguments. He contends that the reverse is true, *i.e.*, the early fusion is the result of shortening of the base and not the cause. The changes in the skull, in other words, are according to Jansen largely mechanical malformations due to infolding which are of much greater moment than the trophic disturbances. A participation of the nasal and ethmoid bones in this process accounts for the deformity of the nose. Prognathus is also associated with these changes. Dentition is seldom abnormal. In the most severe cases the sella turcica is often greatly reduced in size (Jansen).

The vertebral column rarely escapes but the alterations are not very noticeable. Jansen says that the vertebrae diminish in size from above downward which is the exact reverse of the normal spine. A dorsolumbar kyphosis can always be demonstrated (Fig. 16). Wheeldon[35] has recently described a "wedged shaped vertebra" in several achondroplastic children which he interprets as a result of amnion pressure.

Porak[21] particularly emphasizes the fact that the trunk shows a normal

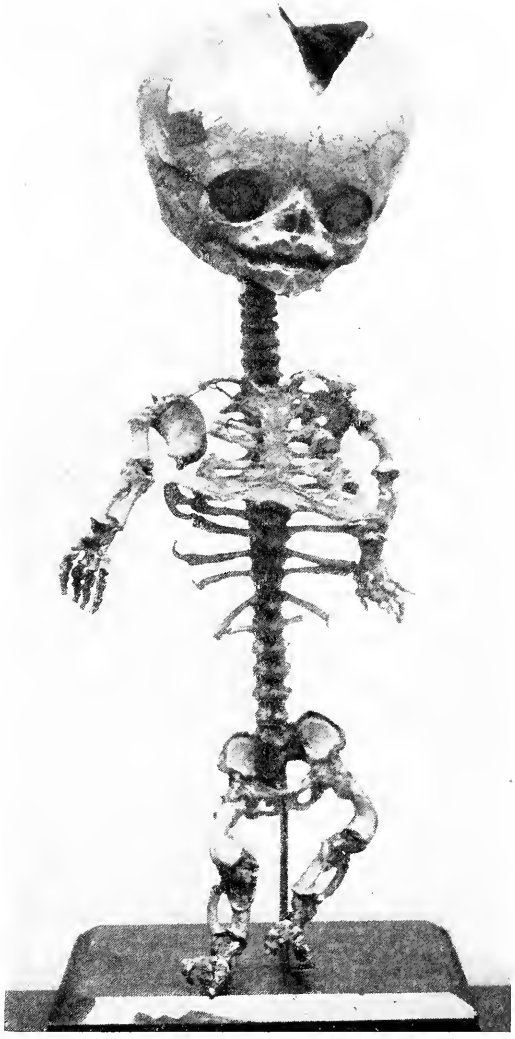

FIG. 15.—Achondroplasia. Skeleton of seven months foetus. (Warren Museum, Harvard Medical School.)

A. *Facing* 480

FIG. 16.—Achondroplastic Dwarf.

Age 23, height 3 feet 10 inches.

development. This is true in many cases and the changes in the thorax are never striking but nevertheless alterations indicating arrested development in the ribs do occur. The thorax is sometimes small above and broadened below. A projecting sternum and flattening of the chest have been observed. Several authors have described a well marked rosary similar to the rachitic rosary but the enlargement at the junction of the cartilage and ribs is not, as is the case in rickets, due to cartilage proliferation but to bony overgrowth from the epiphyseal cartilage of the rib (Frangenheim[8]). This thickening is more marked on the inner thorax wall than the outer. The clavicle and scapula usually escape noteworthy changes except that they are apt to be somewhat below the normal in size. The same general type of changes resulting from arrested bone development is seen in the pelvis. It is misshapen and flattened as a result of early synostosis and arrested osseous growth. The sacrum and coccyx develop normally.

The most remarkable and interesting changes are found in the bones of the extremities, especially the femur and humerus (Figs. 17 and 18). In general these long bones show first of all a shortening of from one-third to one-half in length in which the epiphysis does not participate (Frangenheim). The fibula, however, as first mentioned by Marie is relatively longer than the tibia. The diameter of the diaphysis is not far from the normal thus giving to the bones a very short but massive appearance. The shaft may be straight but is more often curved to a pronounced degree. As the bones are hard and compact fractures are but very rarely seen. The malformation in the epiphysis is quite as striking as that of the diaphysis. This portion of the bone shows an enormous hypertrophy which takes the form of an irregular mushroom growth. In consequence of this cartilaginous overgrowth motion in the joints of the extremities is often limited and sometimes entirely lost. More or less flexion is the rule. The joint surfaces are normal and arthritis does not occur. Notwithstanding the fact that the bones of the hands and feet develop from cartilage the involvement in them is not very conspicuous.

On section the affected bones present very abnormal and varied appearances. There is evidence that periosteal bone production is active where endochondrial ossification is wanting. The cortex of the shaft is thickened and the periosteum active. Many osteoblasts are present. For the most part a fairly regular system of trabeculae is found. The medullary canal is often wanting but the marrow spaces are numerous and enlarged. The marrow is vascular and rich in round and spindle cells as well as red blood corpuscles. Giant cells are sometimes abundant suggesting bone absorption. Bone absorption does occur and may progress to such an extent that fractures take place but such an occurrence is rare. Osteosclerosis occasionally complicates the picture.

The huge cartilaginous ends of the bones show even greater changes

than are found in the shaft. In some cases the tissue has the structure of normal hyaline cartilage in a state of active growth. More commonly the cartilage structure is grossly abnormal. MacCallum[15] describes "a peculiar disappearance of the normal homogeneous matrix, so that the cartilage cells are single or in little groups which hang together in a network." Connective tissue metaplasia is common. Vacuolation has frequently been mentioned. The most important and characteristic change in the cartilage in chondrodystrophia foetalis is the marked aplasia in the zone of ossification. Kaufmann[13] says "in all cases there is a more or less complete inhibition of the normal row formation of the proliferating cartilage cells in the preparatory stage of ossification." It is this aplasia in the zone of proliferating cartilage at the epiphyseal line which explains the diminution in the power of length growth in the long bones. A peculiar and constant lesion in all severe cases is the continuation of the periosteum inward for a variable distance between the diaphysis and epiphysis. It was first noted by Urtel[31] who regarded it as a factor in limiting the endochondrial bone formation.

In a considerable number of cases lesions of other tissues and of the internal organs have been reported but they are too varied and inconstant to suggest that any are characteristic of achondroplasia.

Varieties

Mention was made above of the anatomic classification suggested by Kaufmann of achondroplasia into three general groups, *viz.:* (1) chondrodystrophia hypoplastica, (2) chondrodystrophia malacica and (3) chondrodystrophia hyperplastica. Variot[32] also divides the disease into the hypoplastic (achondroplasie vraie of Parrot) and the hyperplastic forms in accordance with differences seen in X-rays of living cases. Regnault[25] speaks of limited forms of the disease in which the skull alone or the skull and the upper extremities are the only parts involved. Dufour[4] describes an atypical form. Jansen[11] contends that achondroplasia appears in varying degrees and that the forms described by Regnault and Dufour are really mild forms of the disease. Patients may show symptoms typical of chondrodystrophia but limited to only a portion of the body. It seems probable that the various types described are only different grades of the same disease. As a rule it is only the mild cases which survive and these seem to conform in a general way to the hypoplastic form of Kaufmann. Opie and Allison[18] have recently published a careful study of two cases and conclude that their "observations establish the occurrences of hypertrophic chondrodystrophy as a disease of postfetal life, and show that associated abnormal endochondral osteogenesis may persist throughout adolescence."

Certain changes in the soft tissues seen in achondroplasts strongly sug-

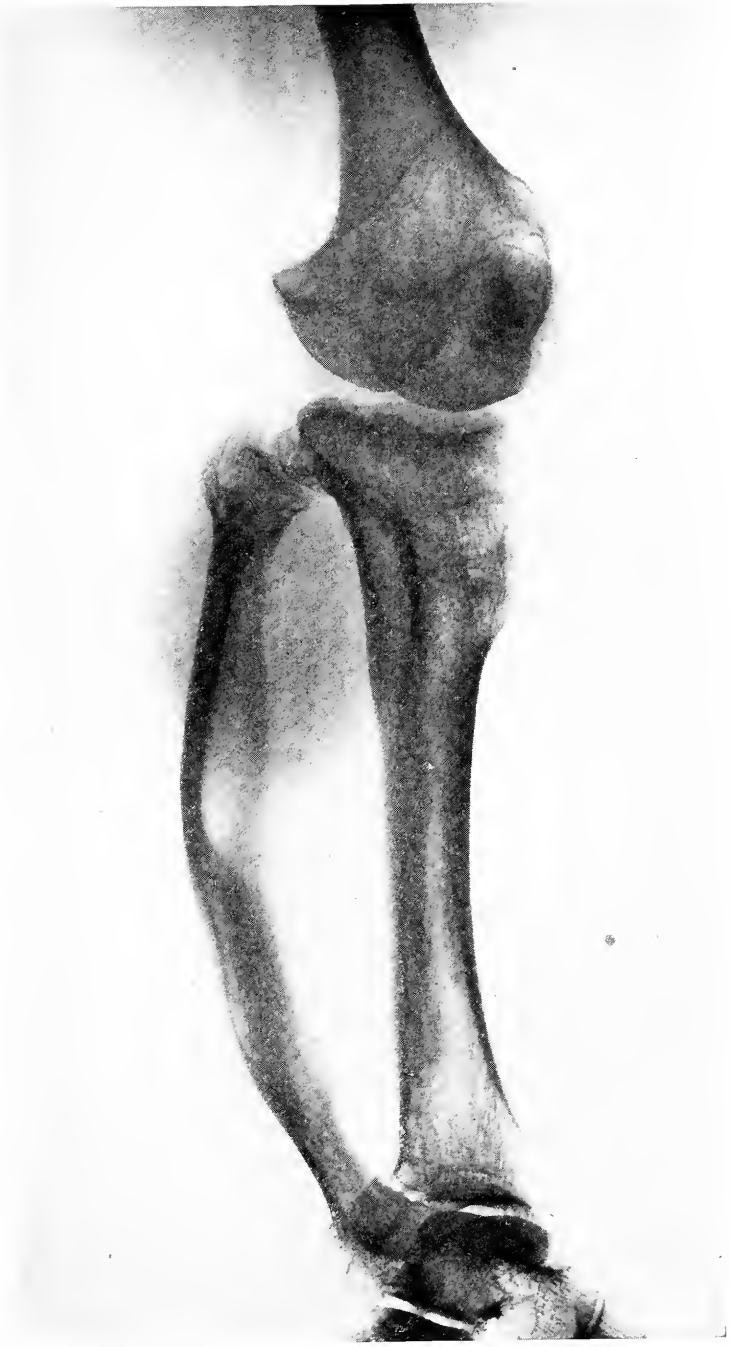

FIG. 17.— Achondroplasia. X-ray of lower leg of patient shown in Figure 16.

A. *Facing* 482

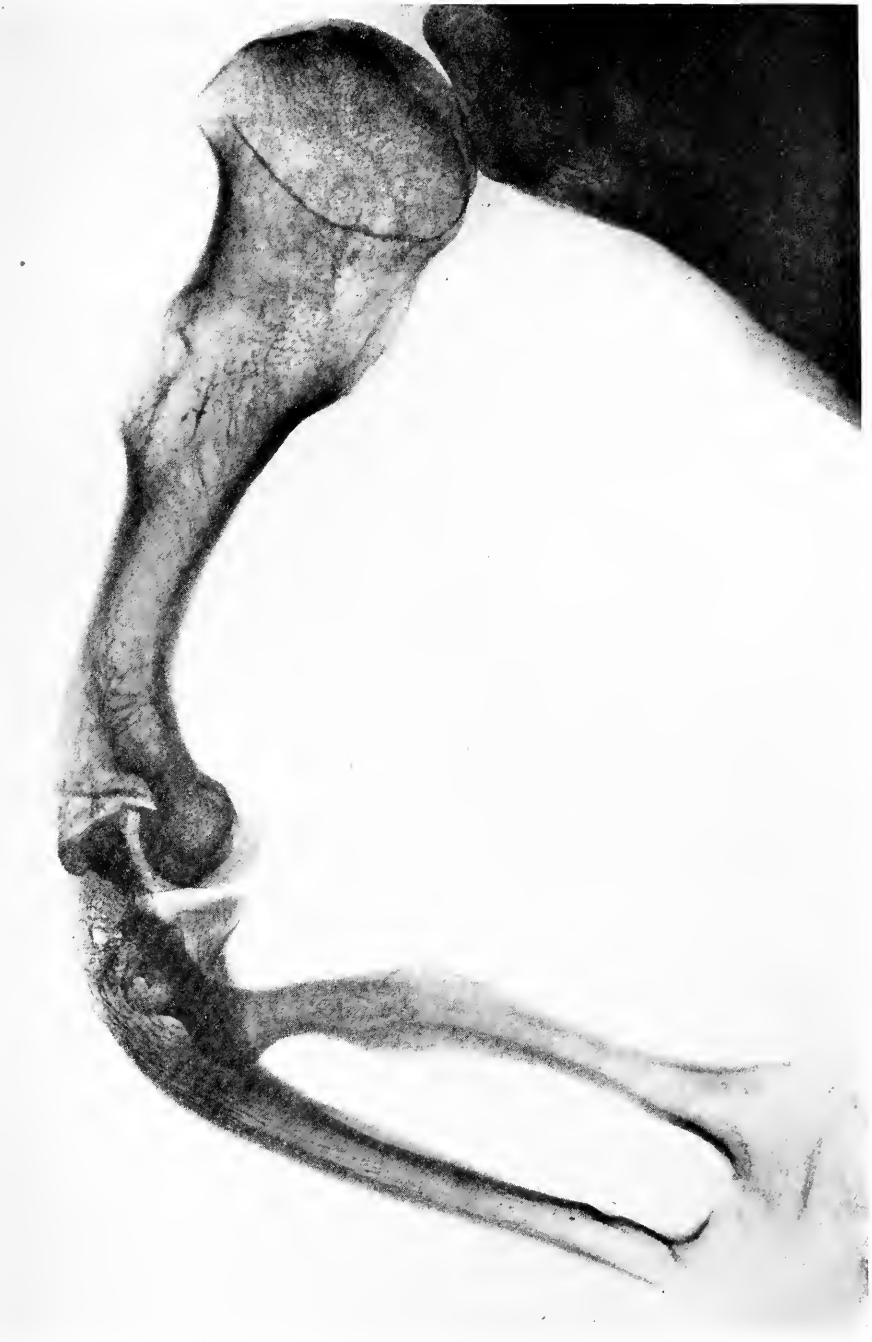

FIG. 18.—Achondroplasia. X-ray of arm of patient shown in Figure 16.

gest a close relationship between the disease and cretinism. Symmers and Wallace[30], in 1913, studied five cases of fetal chondrodystrophy and claim to have established the fact that at least in a certain proportion of cases there is an intimate association with cretinism. Significant pathological lesions in the thyroid gland were demonstrated in all of their cases. There is no evidence, however, that the cretinism bears any causal relationship to the changes in the skeleton.

Symptoms

The symptoms are essentially objective and have already been mentioned under pathology. The moderately large head of the brachycephalic type, rather small and cretinoid features, depression of the root of the nose, prognathus, normally developed trunk contrasting with the short and plump extremities, lordosis, trident hands, protuberant abdomen, general increase in the subcutaneous fat and loose integument are constant features of the achondroplastic fetus. With very rare exceptions these infants are still-born or die in the early months of life. The few who survive the first year or two develop without impairment of their general health and apparently have the same expectation of life as do normal individuals. The great majority of adult dwarfs are of this so-called achondroplastic type.

In early years the adiposity disappears and the skin gradually takes on a normal appearance. The fetal deformities of the skeleton persist but otherwise the development of the child is essentially normal. Except for occasional instances of hyperplasia of the teeth, dentition is not defective. Organic functions are normal. Kassowitz[12] mentions a relaxed condition of some of the joints and especially the knees but such an occurrence is the exception. Opinions differ widely as to the mentality and disposition of these cases. Ballester[2] says "such patients are docile, kind, subnormal in intelligence, credulous as children and obedient." By others they are said to be ill-tempered, quarrelsome, lascivious and to possess an infantile intellect. It is evident from a study of the reported cases that the mentality and disposition vary considerably but in the vast majority seem to be normal. Sexual growth as a rule progresses as in other children although a few instances are on record of an extraordinarily early development.

The adult achondroplast is a deformed dwarf and with slight modifications due to growth presents the same general characteristics as are seen in the fetal stage (Fig. 15). The same decentralization of the body is present, the central point being at the zyphoid cartilage or slightly higher instead of at the symphysis pubis as is the case in normal adults. A very striking feature is the abnormal development of the skeletal muscles, which gives the achondroplastic dwarf a strength relatively much greater than the normal

man. The posture is erect and the spine perfectly straight except in the lumbar region where there is marked lordosis due to the forward tilting of the sacrum. Emerson[7] gives the average height of eighteen achondroplastic males as 119 cm. and of eighteen women as 116 cm. The ratio of the circumference of the head to the total body length is much greater than in individuals of normal stature. A decided brachycephalic or globular type of head (increased cephalic index) and prominence of the frontal and parietal portions are constantly present. The face is actually large but appears small in consequence of the enlarged calvarium. All of the features are somewhat coarse but the nose in particular shows constant changes. The whole nasal region is flattened with an especially well developed retraction at its root. The end is hypertrophied and rounded. The extremities are symmetrically and about equally involved, but in both the arms and legs the greatest shortening is in the proximal or root segment (rhizomelia). Relative shortening of the tubular bones increases with growth and the disproportionate size of the epiphyses becomes more marked. The arms are so much shortened that the finger tips which normally reach to the mid thigh barely touch the crest of the ilium. Complete extension of the elbow joint is impossible and motion in the shoulder articulation is usually somewhat limited. The bones are only slightly curved. The hands are diminutive, short, broad and pudgy. All of the fingers are of about equal length and tapering, and distal to the second joint are separated from each other like the spokes of a wheel or trident; hence the name "main en trident" (Marie). Equally marked dwarf characteristics are present in the legs and the femur and tibia are apt to show considerable bowing. Malposition of the knee joint and relaxation of the joints of the toes are common.

The sexual organs are normally or overdeveloped while an exaggeration of sexual functions is not unusual. This enhanced sexual appetite is common to both sexes. A considerable list of abnormalities may be cited as occasionally seen in achondroplasia. Jansen considers harelip, micrognathy and agnathy, myxedema and hydrocephalus as non-characteristic symptoms of the disease.

X-rays show particularly characteristic appearances in achondroplasia which are unlike those seen in rickets and cretinism, the two conditions with which the disease is sometimes confused. They confirm the pathological findings as regards the size and shape of the affected bones. Fussel and Pancoast[9] have described the abnormalities in growth of the epiphysis and shaft as well as in osseous structure. They consider the appearances in the hands and feet especially as peculiar and unique. The abrupt expansion of the shaft at its epiphyseal end and the deficient and irregular ossification at this point are important features. A localized and very abrupt bowing at the upper end of the tibia and lower end of the femur also contrasts with

the broad curve of rickets. The shaft of the long bones is dense and fairly uniform. All ridges for the attachment of muscles are enlarged and the normal angles accentuated.

Course and Prognosis

Nearly all cases die between the seventh and ninth month of intrauterine life. Of those living at birth the majority succumb within the first few months. The few who survive the first year, probably representing the mild type of the disease, seem to have a normal chance of life. In spite of the dwarfism these individuals often possess a physical vigor considerably above the normal. Numerous cases are found in the literature who have lived to extreme old age. Since achondroplasia is primarily the result of deficient bone growth the disease does not advance after the time when bone growth normally ceases.

Diagnosis

The principal diagnostic features of achondroplasia are the fetal origin, macrocephalic and brachycephalic head, depressed root of nose and prognathus, normal trunk, stunted growth of the extremities with resulting decentralization of the mid point of the body, bone deformities, lordosis, "main en trident," general excess of subcutaneous fat with thickened, loose skin, protuberant abdomen, normal mentality and the X-ray findings. If these characteristics are kept in mind achondroplasia should never be confused with any other condition.

The differentiation from osteopsathyrosis is discussed under that disease. Mongolism bears no real resemblance to achondroplasia. The subject of the former is an idiot, shows facial characteristics entirely unlike those of achondroplasia and suffers from none of the skeleton changes of the latter. Cretinism is sometimes confused with this disease since the chondrodystrophic infant often presents certain changes in the face which are suggestive of cretinism. The cretin is feeble minded and shows the objective signs of myxedema. Rickets is probably a rare complication of achondroplasia in children but bears no close resemblance to it. The X-ray findings will differentiate the process in the bones in the two conditions.

Treatment

Beyond the employment of measures to improve the general nutrition treatment is of no avail.

Part VII

HEREDITARY DEFORMING CHONDRODYSPLASIA (MULTIPLE CARTILAGINOUS EXOSTOSES)

Introduction

Definition.—This is an hereditary disease of congenital origin showing as its most characteristic features multiple cartilaginous and osteocartilaginous growths, chiefly on the metaphyseal portion of the bones, and secondary skeletal deformities resulting from early developmental defects.

Synonyms.—Multiple cartilaginous exostoses (Virchow); hereditary multiple exostoses; multiple cancellous exostoses; ossified diathesis; rhachitiform enchondrosis; exostoses epiphysaires nombreuses; exostoses ostéogéniques multiples, or héréditaires or familiales (Curtillet); exostoses juxtaepiphysaires; exostoses congénitales symmétrique nombreuses; dyschondroplasia; Wachstums-exostosen; chondral or exostatic dysplasia (Kienböck); multiple congenital osteochondromata (Boggs); hereditary deforming chondrodysplasia (Ehrenfried); diaphysial aclasis (Roberts); multiple cancellous osteomata (Lett); multiple chondroosteomata (Percy); dystrophia ossea congenita (de Josselin and de Jong). The term, hereditary deforming chondrodysplasia, suggested by Ehrenfried[4], best describes the disease, but the most commonly employed designation is multiple cartilaginous exostoses.

Among the very early anatomical writings the exostoses were repeatedly described as interesting bone anomalies but the recognition of the condition as a definite disease did not occur until much later. During the past hundred years a large number of cases have been reported and the condition much studied, though until very recent years almost exclusively by the French and German authors. The first case recorded in this country was reported by Gibney[8] in 1875. A very exhaustive and critical review of the voluminous literature was published by Frangenheim[7] in 1912. In 1915 Ehrenfried[4] was able to collect approximately six hundred cases reported in three hundred articles. The same author[6] in 1917 assembled ninety-nine from the American literature. The large number reported in very recent years and especially the relatively large series personally studied by various authors indicates that the affection is not rare. This illustrates what so often happens, namely, that rarer diseases are often overlooked because not considered among the possibilities.

Etiology

Little is known regarding the etiology of the disease. Numerous theories to account for the peculiar bone changes have been suggested. The disease has been attributed to bacterial infections, syphilis, rickets, disturbances of the central nervous system and trophic nerves, and to abnormal function of the endocrine glands, especially the thyroid, but none have the support of clinical or experimental evidence and it seems evident that the disease does not find its origin in any of these factors. The most probable hypothesis is that multiple cartilaginous exostoses represent a "disturbance in development of the intermediary cartilage due to an original defective anlage" (v. Bergmann[3]). In elaboration of this view Keith[10] quotes Hunter's teaching regarding the nature of bone growth. He described a double process, first, the laying down of new osseous tissue in the diaphysial lines and second, the new bone rebuilt structurally and made a part of the shaft. According to Keith this "modeling process" is arrested in hereditary deforming chondrodysplasia. This defective evolution in bone growth is usually termed chondrodysplasia.

Age.—The process in the bones is definitely associated with the period of bone development and probably in all cases begins in early infancy. In the early stages the presence of the exostoses may be unrecognized unless shown by the X-rays but with bone growth in subsequent years the tumors gradually increase in size. The chief manifestations of the affection seldom appear prior to the fourth to sixth year and often not until later. The age period at which the exostoses are usually first noted has been studied by Honeij[9] in sixty-six cases; fourteen were between one and ten years, seven between ten and fifteen years, eleven between fifteen and twenty years, nine between twenty and twenty-five, ten between twenty-five and thirty, and fourteen over thirty years. X-ray examinations in a considerable number of cases make it seem evident that by this means the early lesions can be demonstrated soon after birth.

Sex.—The disease predominates in the male sex. In eighty-nine cases Ehrenfried[6] found a ratio between the males and females of 3:1. Percy's[13] ratio of males to females among the thirty members of a single family investigated for four generations was 5:1.

Heredity.—The condition is clearly hereditary. Among two hundred and thirty-six cases studied by Ehrenfried[4] direct heredity was found in one hundred and seventy-six and this author concludes "that familial occurrence is demonstrable in the majority of cases." In seventy-six cases collected by him, where special inquiry was made regarding inheritance, positive evidence was found in sixty-three occurring in ten families, or eighty-

three per cent. Reinecke[15] investigated thirty families having members with exostoses and found the disease present in two, three, four and five generations. Percy[13] traced one exostotic family through four generations. Among the one hundred and thirteen individuals twenty-five males and five females, or 26.5 per cent., were found affected. Ehrenfried[6] reports eight cases in three generations comprising eighteen individuals.

Transmission of the disease is more frequent through the males, in which sex it predominates, but there is no case on record where transmission has taken place through an unaffected male as may occur through an unaffected female (Ehrenfried[6], Reinecke[15], Ashhurst[1]). The inheritance is usually immediate from parent to offspring. The parent may have enchondromata and the child true exostoses, or the reverse may occur.

Pathology

The pathological changes in the bones in this disease present a very complex and somewhat confused picture depending on the extent and severity of the process. The gross lesions may be grouped, (1) as those associated with the formation of chondroma or osteochondroma, and (2) those resulting from arrested bone development. Perrin[14] speaks of the exostoses and disturbances of growth in hereditary deforming chondrodysplasia as "different manifestations which are habitually associated and with parallel evolution." There appears to be abundant proof that the cause of the bony outgrowths as well as the deformities due to growth retardation lies in a disorder of the intermediary cartilage, *i.e.*, a chondrodysplasia, affecting chiefly the metaphysis of the long bones and to a less extent the scapula, clavicles, spine, ribs and pelvis. The origin of osseous abnormalities, in other words, lies in a "disturbance in the proliferation and ossification of the intermediary cartilage during the period of growth" (Ehrenfried[4]). This fact explains the absence of changes in the bones of the face and cranium which develop from membrane.

The microscopic appearances of the cartilage are those of a greatly disordered and excessive growth. Throughout the area between the epiphysis and diaphysis (zone of proliferation) are irregular masses of cartilage cells without orderly arrangement and with only incomplete ossification in occasional groups. The intermediary cartilage itself is often thin and very irregular in outline as in the case of the cartilage at the distal end of the radius. In some cases very early ossification of the cartilage occurs leading to premature union of the epiphysis and diaphysis. According to most authors the epiphysis is but little if any changed except in the more severe cases where it is often considerably distorted and di-

minished in size. Honeij[9] in a roentgenological study of four cases found rather striking enlargement in the epiphyses and concludes that moderate metaplastic changes frequently occur and even unrestricted growth may rarely take place. The periosteum of the affected bones is to a moderate degree thickened and shows evidence of abnormal activity. Here and there beneath the periosteum near the end of the bone are seen nests of uncalcified cartilage cells.

The most characteristic changes in chondrodysplasia concern the metaphyseal portions of the long bones and especially of the femur, tibia, fibula, ulna and radius. The essential lesion in these locations is a striking overgrowth of bone which appears as an extremely irregular, ragged, often cauliflower-like proliferation of the bone(Fig. 19). It may encroach slightly on the epiphysis and even interfere with free movement in the joint. Except for the ends of the shaft the structural alterations in the diaphysis are not significant.

Exostoses are the most striking feature of the disease (Fig. 19). They may be few in number or exceedingly numerous. In Woodward's case (see Turner[16]) one hundred and eighty tumors of the skeleton were counted during life. They vary in size from a small spur to a tumor of many centimeters in diameter. Their distribution is in general symmetrical but instances of a more or less strict unilateral arrangement on the skeleton have been recorded. The location of the tumors is almost exclusively on the diaphysial ends of the bones, though small ones do develop along the central portion of the shaft. The parts forming the knee, ankle, hip and wrist are the most frequent sites. In outer form the exostoses are extremely varied but commonly are irregularly rounded or lobulated. The exostoses are covered with dense cartilage and may show bursae on their outer surface. Small portions of the tumor sometimes become separated and remain in the bursa as floating bodies. True enchondromas are often associated with the exostoses. Both the enchondromata and the exostoses take their origin in the cartilage formed at the epiphyseal line, small islands of which through a process of infolding may become separated with and the bone growth carried along under the periosteum. If excessive growth in the lower end of the tibia or ulna occurs a pseudarthrosis or synostosis with the companion bone often results.

On section the tumors are seen to be covered with a thick glistening cartilage throughout. Beneath the enveloping cartilage is a layer of hyaline cartilage and osseous tissue of variable thickness. In this layer some trabecular structure is present. The central portion of the growth contains more lime salts and the denser bone is continuous with the underlying cortex. The presence of marrow spaces and an actual lamellar arrangement like normal bone is described by some. The interior of the tumor

is sometimes rich in connective tissue and blood vessels. As the result of fracture the exostosis is occasionally separated from the bone and becomes a floating body.

Skeletal growth retardation forms a less conspicuous part of the disease but is regarded by many authors as the essential feature (Lenormant[12], Bessel-Hagen[2], Perrin[14], Ehrenfried[5], Ashhurst[1], Honeij[9] and others). The results of arrested growth in mild cases are so slight as to be difficult of demonstration but in all severe cases are clearly marked. Their distribution is the same as the exostoses since both have a common origin in the chondrodysplasia. The slight shortening of the legs produces a corresponding lessening in stature but it is much less marked than in achondroplasia, the central point of the body being only from one to two inches above the symphysis. Well marked dwarfism as seen so commonly in the latter disease does not occur in multiple exostoses. Bessel-Hagen[2] designates the shortening of stature as partial dwarfism in contrast to the marked dwarfism seen in achondroplasia. With but few exceptions the length growth in the individual bones is nearly normal, the retardation being confined largely to the development in size and particularly the metaphyseal part. The deformities are more regularly symmetrical than is the arrangement of the exostoses and enchondromata. A very noticeable shortening of the fibula often occurs and may be so great as to disturb its relation to the ankle joint, thus producing the deformity pes valgus, or rarely pes varus. Knock knees are seen with equal frequency. Striking growth changes in the upper portion of the femur are characteristic of the disease. A complete synostosis between the fibula and tibia at either end is frequently found and rarely a pseudarthrosis between the same bones (Fig. 19). This is also true of the ulna and radius. In consequence of the shortening of the ulna this bone may not articulate with the carpus but form a false articulation with the radius in its lower third or become firmly united with it. The hand is then deviated to the ulnar side (Fig. 20). A peculiarly characteristic deformity in the ulna is a pointed distal end, the so-called arrowhead form (Fig. 20). These changes in the ulna are accompanied by constant deformities in the radius which as a result of the shortening of the former becomes bowed or less frequently dislocated at its upper end. A rosary is often present and Ehrenfried[5] has observed a caving in of the chest wall. The spine seldom shows other deformities than a slight scoliosis. The carpal and metacarpal bones less frequently show variations in length, size and outer form as also do the corresponding bones of the feet. Analogous changes take place in the pelvis and scapulae, the acromion process of the latter being disproportionately large and the glenoid fossa small. Cystic degeneration is by no means rare and actual necrosis probably takes place but is unusual.

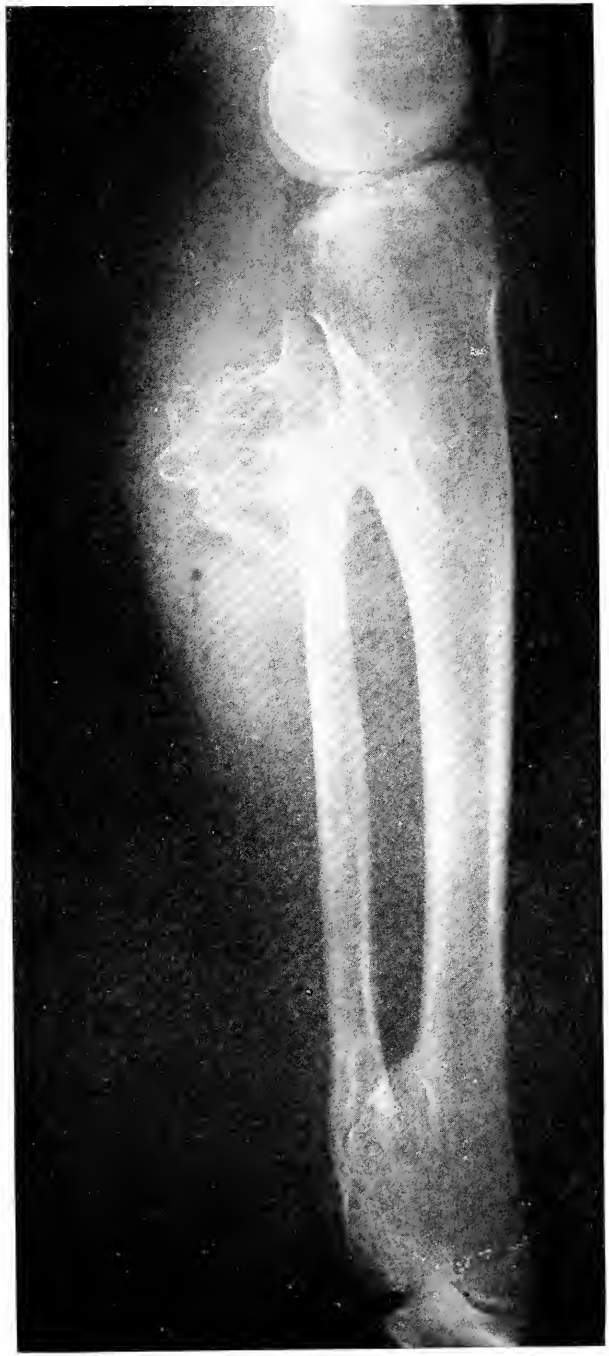

FIG. 19.—Hereditary deforming chondrodysplasia. Male, age 19 years. X-ray of lower leg showing large exostosis at upper end of fibula and synostosis between fibula and tibia in their lower portion. (Case of Dr. A. Ehrenfried.)

A. *Facing* 490

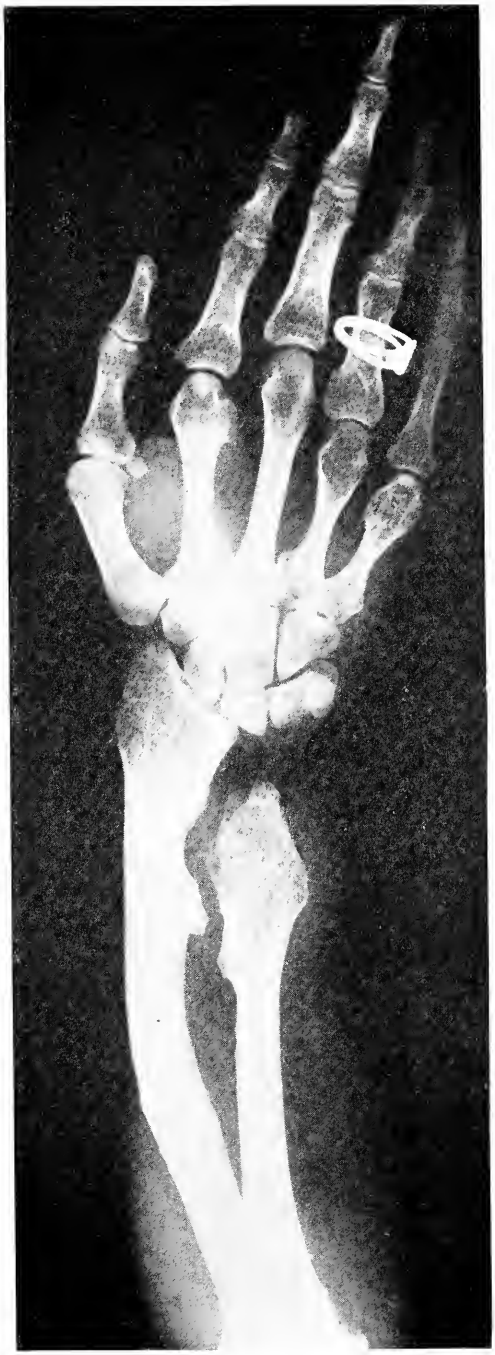

FIG. 20.—Hereditary deforming chondrodysplasia. Male, age 20 years. X-ray of forearm and hand, showing shortening of ulna with characteristic deformity of distal end and bowing of the radius. Note the ulna deviation of the hand. (Case of Dr. A. Ehrenfried.)

B. *Facing* 490

While the joint tissues are not directly involved, many of the articulations show distortions or, in consequence of the presence of the exostoses in the adjacent bones, limitation of motion is present. Disturbed functions of such a mechanical nature are particularly prone to occur in the ankle, knee, hip, elbow and wrist.

Metabolism

Krieble and Bergeim[11] studied the nitrogen, sulphur, calcium, magnesium and phosphorus metabolism in a girl of fifteen suffering from multiple cartilaginous exostoses. The most striking abnormality found was a loss of twenty-one and eight-tenths per cent. of the nitrogen ingested. The authors suggest that the loss of nitrogen and decrease in weight were probably due to a severe gastrointestinal disturbance with diarrhea from which the patient suffered. In spite of the negative protein balance the subject gave a positive sulphur balance. The retention of sulphur is probably to be explained as due to the extensive cartilage formation which is a tissue rich in sulphur. There was a retention of calcium, magnesium and phosphorus although the excretion of these substances in the urine was normal.

Underhill, Honeij and Bogert[17] have very recently investigated the calcium and magnesium metabolism in two cases representing respectively the stabilized and progressive stage of the disease. In the former stage the calcium exchange was normal and the magnesium excretion two or three times the normal when the patient was on a diet either rich or poor in these elements. In the progressive stage the calcium metabolism was essentially normal irrespective of the amount of calcium in the diet. The ratio of elimination by the urine and feces was also normal. The excretion of magnesium in the progressive stage resembled that of the stabilized stage but the percentage of elimination was somewhat less.

Symptoms and Clinical Characteristics

The disease shows no primary symptoms and even the marked skeletal deformities seen in the severest types of cases give but few secondary symptoms. Such symptoms as do occur are largely the result of complications arising from the tumors and distortion of the long bones. Pain and tenderness over the tumors are never present except as a result of secondary changes such as ulceration, or inflammatory complications. There are no constitutional manifestations of the disease or changes in the blood and excretions. In consequence of the absence of symptoms and the latency

of the process the presence of the disease is seldom recognized until late in its course. The patient rarely consults the physician except for some complication.

In contrast to the paucity of symptoms the objective signs are usually prominent and occasionally striking. The bony outgrowths are very apparent and may present quite extraordinary appearances. The deficient growth of the fibula with relative overgrowth of the tibia often leads to the development of pes valgus and a similar growth anomaly on the part of the radius and ulna to marked deformity of the wrist with ulna deviation (Fig. 20). As a result of such deformities the posture is abnormal. Mechanical limitations in the joints, particularly the wrists, elbows, hips, knees and ankles, are frequent and sometimes very marked. Bessel-Hagen[2], Perrin[14], and Ehrenfried[5] have emphasized the constancy of a slight to moderate diminution in height which is chiefly confined to the lower extremities. The central point of the body is therefore raised as in achondroplasia but to a much less degree. The central point is never more than one or two inches above the symphysis.

By roentgenographic examination the tumors and bone deformities described under pathology can be readily demonstrated. The appearances in the tumor growths are extremely variable depending on the amount of osseous tissue present. Some are extremely dense and others very transparent. Honeij[9] has made a special study of the skeleton in several cases by this method and finds evidence of a rather general but not constant change in structure in the bones showing exostoses and marked deformity. In a few bones the density of the shaft is increased but a more common and characteristic abnormality is an increased transparency and longitudinal penciling of the shaft.

Complications

By reason of their rarity complications are of minor importance. The most serious complication is the development of malignant osteochondromata which occurs in a very small percentage of cases. Fractures secondary to trauma and spontaneous fracture of an exostosis have been noted in a few instances. Ehrenfried[5] collected eight cases with erosion of a blood vessel by an exostosis and resulting aneurysm. Pressure on nerve trunks can cause neuralgia or paralysis and compression signs in the cord may be caused by intraspinal exostoses. The pelvic deformities have been known to interfere with childbirth. Unusual complications such as pressure abscess, epilepsy, apoplexy, and defective hearing are sometimes mentioned.

Course and Prognosis

The exostoses show a more or less regular development throughout the period of skeletal growth, ceasing with skeletal maturity. A few authentic cases have been collected by Ehrenfried[5] in which growth continued in the exostoses for considerable periods after the age at which bone growth ceases. When growth stops the exostoses and the deformities as a rule become fixed but a considerable degree of retrogression is possible. The general health of the individual with chondrodysplasia is not impaired and the occasional complications are seldom dangerous to life.

Diagnosis

The special features important in diagnosis are, (1) multiple cartilaginous exostoses showing for the most part a juxto-epiphyseal position, (2) evidences of slight growth retardation in the bones and (3) the X-ray characteristics, especially those about the knee and wrist, described above.

The typical case bears no real resemblance to any other disease. The congenital origin, the changes in the intermediary cartilage and the dwarfism which are common to both achondroplasia and chondrodysplasia suggest some relationship between the two diseases. This seems hardly probable, however, as clinically they are two entirely distinct diseases with no common deformities except for the slight tendency to inhibition in bone growth in multiple cartilaginous exostoses which simulates the mildest forms of dwarfism seen in achondroplasia.

Treatment

Orthopedic measures may give relief in certain cases with pressure symptoms. Surgical removal of the bony growths pressing on nerve trunks or interfering with joint function has frequently been done with excellent results. Every effort should be made to build up the general vitality of the patient. No drug has any effect on the disease.

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